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Getting a Say

Bringing patients' views on benefit-risk into medical approvals

KARIN SCHÖLIN BYWALL

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Abstract
Schölin Bywall, K. 2021. Getting a Say. Bringing patients' views on benefit-risk into medical approvals. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1732. 72 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-1168-5.

The focus of this thesis is a new quantitative approach to consider patient preferences on benefits and risks in medical approvals. The overall aim of this thesis was to explore how patient preference information may be relevant to regulatory marketing authorisation decisions.

Study I provides an overview of the different decision-processes of industry, regulatory agencies and health technology assessment bodies/reimbursement agencies along the medical product lifecycle. In total, 15 decision points with the potential to include patient preference information were identified.

Study II was an exploration of the patient perspective regarding the use of patient preference information in regulatory marketing authorisation decisions. Patients emphasised the need to have a say in decisions affecting their health and to be properly informed about potential risks and benefits of medical products.

Study III assessed patient preferences on benefits and risks of Rheumatoid Arthritis treatments. Results revealed that patients' preferences differed substantially. The three most important treatment attributes for patients with rheumatoid arthritis were: the probability of severe side effects, treatment effectiveness and route of administration. Those placing relatively more importance on treatment effectiveness were willing to acceptance higher risk levels of side effects.

Study IV aimed to determine the influence of an educational tool, compared with traditional written information on patient preferences. It was found that those respondents receiving the educational tool focused more on the potential side effects than those receiving written information.

Patient preference information has the potential to reveal patients' preferences on benefits and risks with scientific rigour and can therefore be weighed against clinical data. This thesis supports the development of a structured approach to learn about patient preferences on benefits and risks in medical approvals

Keywords: Educational material, Medical product lifecycle, Patient preferences, Regulatory marketing authorisations, Rheumatoid arthritis

Karin Schölin Bywall, Centre for Research Ethics and Bioethics, Box 564, Uppsala University, SE-751 22 Uppsala, Sweden.

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List of Articles

This thesis is based on the following articles, which are referred to in the text by their Roman numerals.

I Whichello C*, Bywall KS*, Mauer J, Stephen W, Cleemput I, Pinto CA et al. An overview of critical decision-points in the medical product lifecycle: Where to include patient preference information in the decision-making process? Health policy. 2020. doi:10.1016/j.healthpol.2020.07.007. *Shared first authorship.

II Bywall KS, Veldwijk J, Hansson MG, Kihlbom U. Patient Perspectives on the Value of Patient Preference Information in Regulatory Decision Making: A Qualitative Study in Swedish Patients with Rheumatoid Arthritis. Patient. 2018. doi:10.1007/s40271-018-0344-2.

III Bywall KS, Kihlbom U, Hansson MG, Falahee M, Raza K, Baecklund E, Veldwijk J. Patient preferences on rheumatoid arthritis second-line treatment: a discrete choice experiment of Swedish patients. Arthritis Res Ther. 2020. doi:10.1186/s13075-020-02391-w

IV Bywall KS, Veldwijk J, Hansson MG, Baecklund E, Raza K, Falahee M, Kihlbom U. Does being exposed to an educational tool influence patient preferences? The influence of an educational tool on patient preferences assessed by a discrete choice experiment. Patient Educ and Couns. doi.org/10.1016/j.pec.2021.03.013

Contents

Abbreviations

CHMP	Committee for Medicinal products for Human Use
DMARD	Disease Modifying Antirheumatic Drugs
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HTA	Health Technology Assessment
IMI	Innovative Medicines Initiative
JAK	Jansu Kinase
LCA	Latent Class Analysis
MAB	Minimum Acceptable Benefit
MNL	Multinomial Logit
MPA	Medical Product Agency
MPLC	Medical Product Lifecycle
PREFER	Patient Preferences in Benefit and Risk Assessments during the Drug Lifecycle
RPL	Random Parameter Logit
UK	United Kingdom
US	United States

Introduction

Medical products are approved on the basis that the benefits outweigh the risks for patients. Patients and decision-makers in the regulatory marketing authorisation process are often different people, and they may have different views on benefits and risks. Therefore, patients should be given a say in decisions affecting their health [1]. Occasionally, patient representatives are invited to share their perspective on benefits and risks; however, they may not be representative of the whole patient population [2]. There is a need for methods to quantitatively assess patient preferences on benefits and risks in order to provide regulatory decision-makers relevant information that can be evaluated along with the clinical data.

The focus of this research is a new approach to consider the patient perspective using a quantitative method to assess patient preferences in order to guide regulators in making better decisions [3]. There have been some recent attempts to introduce quantitative assessments of patient preferences in the regulatory marketing authorisation process [4, 5]. However, there is no structured approach for when and how to conduct patient preference studies or to use the results in marketing authorisation decisions [3]. Quantitative assessments of patients' treatment preferences ask respondents to weigh competing alternatives against each other, characterised as attribute levels to select the best alternative [6]. However, it may be difficult for respondents to evaluate the attributes and attribute levels (benefits and risks) relevant for regulatory marketing authorisations, such as a potential risk [7]. It is uncertain if respondents have understood and reflected on that information when weighing benefits and risks against each other [8].

Several questions need to be asked before patient preferences can be used in regulatory marketing authorisation decisions. There is a need to identify when and how to include patient preferences by exploring the stakeholders' and patient perspectives regarding the use of patient preferences in decision-making. Additionally, methods to inform and assess patient preferences need to be explored in order to strengthen the evidence on the concrete use of patient preferences in regulatory marketing authorisation decisions. The overall aim of this thesis was to *explore how patient preference information may be relevant in regulatory marketing authorisation decisions.*

Background

Medical product lifecycle

A medical product needs to undergo an evaluation process of several steps before it is available to the end-user. The medical product lifecycle starts when a pharmaceutical company engages in research and development. The process is then handed over to a regulatory marketing authorisation agency to evaluate if the potential benefits outweigh the possible risks. This process can only continue if there is a positive decision. Health technology assessment bodies and reimbursement agencies evaluate and assess availability and the pricing of the approved medical product. Medical products on the market are then monitored via post-approval activities carried out by regulatory agencies (figure 1).

Figure 1. Medical product lifecycle

Regulatory marketing authorisation process

The main goal of the regulatory marketing authorisation process is to ensure the safety, efficacy and quality of medical products. The European Medicines Agency has a centralised authorisation procedure in all Member States of the European Union. All Member States of the European Union also have their own national marketing authorisation procedures, working closely with the European Medicines Agency. The process can be divided into three main phases: pre-submission, marketing authorisation and post-authorisation [9]. An overview of the regulatory marketing authorisation process with the different stages is illustrated in Figure 2.

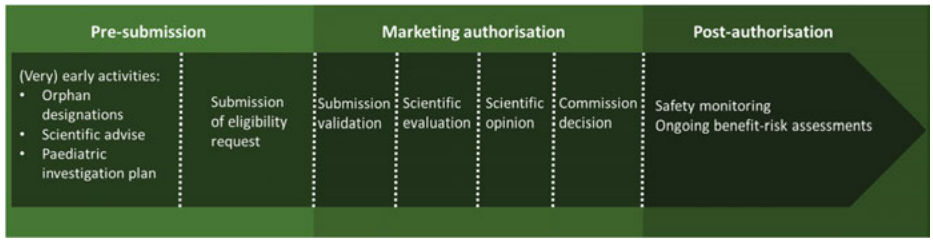

Figure 2. Regulatory marketing authorisation process

The regulatory marketing authorisation process starts when a pharmaceutical company enters the *pre-submission* phase. The first phase may start with *very early activities*, which are not mandatory for all medical products going through the process. Such activities consist of *orphan designations,* which are applied for medical products for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating rare condition or where the product is unlikely to generate sufficient profit to justify research and development costs. *Scientific advice* can be given on the appropriate tests and studies in the development of a medical product. A *paediatric investigation* plan needs to be initiated to obtain the necessary data to support the authorisation of a medical product aimed for children [9].

The next step of a pre-submission is *submission of eligibility request.* In this step, pharmaceutical companies need to consider the date of submission carefully, referring to the submission dates. A responsible committee is assigned at this stage to handle the scientific evaluation. *Submission and validation* are the final steps before entering the marketing authorisation phase to assess the quality of the data. Submission and validation are needed for a new application of a medicinal product, a variation or renewal of the marketing authorisation with specific changes to the approved information. The pharmaceutical company needs to provide safety and efficacy evidence; such evidence is mainly based on results from randomised clinical trials comparing the drug with a placebo, or an accepted comparator, or both, as well as data on identified risks during the pre-clinical and clinical development. All side effects reported by patients or professionals are identified with their frequency and ranked as mild, moderate, severe, life-threatening or leading to death. Pre-submission meetings can be requested to obtain procedural and regulatory advice to enable applications in line with legal and regulatory requirements [9].

The *marketing authorisation* is the central part of the regulatory process, starting with a *scientific evaluation*, when the responsible committee evaluates whether the benefits outweigh the harms of a medical product. The committee issues a *scientific opinion* on whether or not to authorise the medical product. The scientific opinion is based on demonstrated efficacy from well controlled clinical trials following regulatory guidelines, and the benefit-risk assessment shows a sufficient efficacy and a positive benefit-risk balance when used in accordance with the product labelling. The opinion is then sent to the European Commission, which issues the marketing authorisation. A *commission decision* is the formal approval of the European Commission to market a medical product. All commission decisions are published as a European public assessment report. When a medical product is refused, the European Medicines Agency publishes a refusal report [9].

The *post-authorisation* is the final phase carried out when a medical product is available on the market for patients. *Safety monitoring* and *ongoing benefit-risk assessment* activities, such as post-authorisation studies, are carried out after a medical product approval. The committees may conclude that the applicant should provide additional post-authorisation data at the time of finalising a procedure or in follow-up of an evaluation. This information complements the available data with additional data about the safety, efficacy or quality of an authorised medical product. Such post-authorisation measures aim to collect or provide data to support the assessment of the safety or efficacy of medicinal products [9].

Patient input in the medical product lifecycle

Stakeholders in the medical product lifecycle, such as representatives from pharmaceutical companies, regulatory marketing authorisation agencies, health technology assessment bodies, reimbursement agencies, patient organisations and physicians, are evolving towards seeking information from the patient perspective. This is because they believe patients can and should bring in their values in the process [10]. However, the question of how to properly include patients in the process is still unanswered. Several attempts have been made to bring in the patient perspective and values in decisions using different processes [11]. The inclusion of patients in the medical products lifecycle is mainly operationalised by including a patient or a patient representative in a group of experts (i.e. health professionals in clinical care or experts in decision panels deciding on medical product market assessments at a policy level) [12].

The European Medicines Agency's Committee for Medicinal products for Human Use (CHMP) recognises the benefits of including patients in the process. Accordingly, patient representatives are invited to participate in scientific evaluation activities, such as in scientific advice procedures or scientific advisory group meetings, to address specific questions related to medical product development or evaluation of the data submitted to achieve a marketing authorisation [9]. For scientific opinions, patients may contribute to the evaluations concerning the feasibility of a study proposed, relevance of the patient populations, duration of study, relevance of patient outcomes, safety concerns, and feasibility of the risk management plan [13]. Although the perspectives of patient representatives have shown to be informative for regulatory decision-making, their perspectives may not be representative of the wider patient population. Therefore, quantitative assessments of patient preferences that include information from larger populations have greater potential to provide relevant information on patient preferences and the distribution across the population [14, 15].

Patient preferences

Patient preferences may be defined in different ways, depending on the context. For example, in the clinical context, patient preferences are defined as *the evaluation of all domains of healthcare and how it relates to patients*. Clinicians have for long considered patient preferences in clinical care as part of what is now called shared decision-making [16].

The regulatory context, in which the term *patient perspectives* refers to a specific type of patient input, includes information relating to patients' experiences with a disease or medical condition and its management. The patient perspective may be useful in identifying outcomes most important to patients and understanding benefit-risk trade-offs for medical treatment. The term *patient preference information* is used as a specific type of the patient perspective and is defined as *qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions* [10].

Patient preference information may be particularly useful in regulatory marketing authorisation decisions for evaluating the benefit-risk trade-off of medical products when a patient decision is *preference sensitive*. Decisions are preference sensitive when multiple treatment options exist and there is no option that is clearly superior for all patients; the evidence supporting one option over others is considerably uncertain or variable; and/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 [10].

Patient preference information might be valuable in regulatory decision-making in several ways. First, it helps to identify the most important characteristics of a medical product from the patient's perspective. Second, it makes it possible to assess the relative importance of different treatment attributes and to clarify how patients think about the trade-offs of benefits and risks for a given medical product. Finally, it allows for an understanding of the heterogeneity or distribution of patient preferences for various treatment alternatives [10].

Patient preference measurement methods

Patient preferences can be assessed by both qualitative preference exploration methods and quantitative preference elicitation methods. Qualitative preference exploration can be grouped into individual techniques or group techniques, depending on the number of participants and setting. Exploration methods may be suited for early stages of the medical product lifecycle. Examples of this include defining value frameworks, or identifying endpoints or attributes, or exploring subjective experiences and heterogeneous data [17].

The quantitative preference elicitation methods can be used to understand and assess patients' preferences for health states. There are two approaches of preference elicitation: revealed or stated preferences. Revealed preferences are actual choices of people observed in real life. Stated preferences are measured by studies that control the way in which preferences are elicited in hypothetical choice situations [18]. Stated preference methods include conjoint analyses, discrete choice experiments, best-worst scaling, direct elicitation and trade-off techniques [19]. One of the most common stated preference methods is *discrete choice experiments*, which may be used to estimate preferences and predict choices that present respondents with multiple-choice questions. Discrete choice experiments stand on a theoretical base with established good research practice [18]. A discrete choice experiment is relatively difficult for researchers to construct and analyse, and participants may find it burdensome to answer. The *conjoint analyses* approach is used to estimate the value of different attributes and/or levels by using a combination of rating, ranking and choice questions. It is easily available and has a relatively low burden on respondents. However, it can be difficult to explain the method, as it is not sufficiently grounded in choice theory [19].

Best-worst scaling is a relatively simple approach where respondents choose the best and worst items within repeated choice questions. However, there is an uncertainty regarding the ability to predict choices. In *direct elicitation*, participants choose directly from two or more treatments where trade-offs may be explored. It may not be possible to identify the importance of the individual attributes. Direct elicitation may be easy for respondents to answer and explains what participants choose, but not what factors are driving the choice. The *trade-off techniques* use an experimental approach that combines two different treatment options. One of the attributes is systematically varied to identify when participants change their mind. The trade-off techniques are simpler to answer, but they can only explore limited trade-offs (one at a time) [19]. Both qualitative exploration methods and quantitative elicitation methods were used in this thesis (studies III and IV). Attributes and levels to assess patient preferences were identified by using a ranking technique. A discrete

choice experiment was chosen to assess patient preferences and the influence of an educational tool on patient preferences.

Discrete choice experiments

Discrete choice experiments are a choice-based, indirect measurement technique to assess patient preferences [20]. Discrete choice experiments have become commonly used in patient preference elicitation studies to address a wide range of policy questions. The technique allows for quantitative elicitation of patient preferences for healthcare policies, services and interventions [21]. The methodology is based on the random utility theory and consumer behaviour, aiming to quantify the relative importance of attribute levels and to measure heterogeneity within preferences.

The respondent is faced with a set of hypothetical choice questions with two or more alternatives, characterised by different attributes with varying levels [22]. The utility function implies that people derive a certain utility for each choice question, and that the respondent will choose the alternative with the highest utility. However, the utility is latent and cannot be observed; only indicators of utility, such as choices, can be observed. Also, the latent utility consists of a measurable systematic element and a random element that cannot be measured. Moreover, the systematic element includes the attributes together with other measured covariates that determine the respondents' decisions [23]. The utility function can be derived by the equation below.

$$U_{nj} = V_{nj} + \varepsilon_{nj}$$

The latent utility 'U' of respondent 'n' in choice task 'j' can be estimated by taking the sum of the systematic utility element 'V' (i.e. the utility of the respondent 'n' concerning scenario 'j', calculated based on all attribute levels and covariates) and the random error term 'ε' (i.e. all unobserved and unobservable factors that influence the utility of person 'n' concerning scenario 'j'). The systematic element is expected to approximate latent utility. The systematic utility can be calculated by taking the sum of all the attribute level estimates. The level estimates are called 'part-worth utilities'. The relative importance of attribute levels can be concluded by comparing these part-worth utilities. The attribute of which levels represent the largest range in part-worth utilities has the largest impact on utility; therefore, it is reasonably the most important attribute for participants [24].

Patient preferences in marketing authorisations

The growing interest in quantitative assessments of patient preferences in informing regulatory marketing authorisations may be explained by the awareness of the relevance. By using patient preference information in marketing authorisation decisions, which to date is mainly focused on objective clinical evidence, it may be possible to also obtain a patient perspective on factors that typically are not captured in clinical trials [25]. The European Medicines Agency recognises that the views of decision-makers and patients are different, but also that individual patients are different, and they have different preferences. The European Medicines Agency has started to consider the use of patient preferences in assessments of benefits and risks because they believe it enriches marketing authorisation decisions and contributes to the quality of the decisions made [9].

Methods to quantify patient preferences are now under investigation to assess the feasibility and reliability of the data gained by these methods [26]. For example, the European Medicines Agency and the Food and Drug Administration in the United States have launched patient preference initiatives to inform marketing authorisation decisions, with the aim of gaining knowledge on the patients' acceptance of potential risks [11]. According to the European Medicines Agency, assessments of informed patient preferences are particularly valuable in post-authorisations, to help understand how patients weigh potential benefits and risks against each other in a real-world context [1]. Additionally, consistently gathering information about patient preferences during the pre- and post-marketing phases has revealed a potential in improving medical product development and time before access to the market [27].

The relevance of patient preferences for decision-makers depends on the sensitivity of the decision. It may also depend on the level of collaboration across stakeholders in the decision process, the match between the research question, sample and method [28]. There are several factors that need to be considered when designing and conducting a patient preference study to inform decisions in the marketing authorisation process. These are related to the study organisation, study design and conduct of the study [29]. Including patient preferences in marketing authorisation decisions is currently hindered by methodological challenges and lack of guidance on how to handle these challenges. Further best-practice patient preference studies are critically needed to support the development of such guidance [30].

Educating patients for preference assessments

Practical guidance for assessing patient preferences to inform regulatory marketing authorisation decisions suggests that patients should be well-informed when asked to weigh potential benefits and risks of medical products against each other [10]. Usually for patient preference studies, respondents receive some form of educational material to complete the choice questions as well as explanation of the attributes in writing [31], often accompanied by simple illustrations or graphics [32]. However, communicating health information is challenging, and respondents may not understand the information as presented [8]. It is uncertain whether the educational material given to respondents allows them to express their informed preferences. The use of research for this purpose tends to be under-reported in patient preference studies [33]. Educational tools may be useful in this respect. Specifically, they may effectively inform about the decision context, the expected outcomes associated with each option, and provide the opportunity to explore and reflect on different treatment situations.

Educational tools

Adding an educational tool to a preference assessment may be considered when respondents have little or no experience with the choice situation and the attributes; the disease has a high impact on social life, family and daily function; or the treatment is complex and/or the risks involve probabilities, and their impact varies. Educational tools can be useful to explain the different levels of effectiveness and the treatment-related risks, and to help patients to conceptualise probabilities using numeric, verbal or graphic representations of uncertainty. Educational methods to inform patients on potential benefits and risks in assessments of patient preferences have previously been investigated to facilitate shared decision-making [34]. Randomised controlled trials have consistently recognised educational tools to be effective in improving patients' knowledge, decreasing decisional conflict and, in some cases, improving patient participation in shared decision-making [35].

There is no common effective practice to inform patients with rheumatoid arthritis regarding the change of treatment to second-line treatment, or the different available medical products and their characteristics. To address this gap, we aimed to study the influence of an educational tool in an assessment of patient preferences to inform regulatory marketing authorisation decisions. We designed an educational tool to inform respondents of the discrete choice experiment about the disease context and the attributes and levels in the choice questions.

Area of application: Rheumatoid arthritis

The field of rheumatology has revealed an interest in quantitative assessments of patient preferences to inform medical decisions. The interest has recently expanded to policy decisions, such as those relating to regulatory marketing authorisation and the medical product lifecycle [19].

Rheumatoid arthritis was chosen as the area of application for this thesis in order to explore how patient preference information may be relevant to regulatory marketing authorisation decisions. Rheumatoid arthritis was selected because of the many different treatments available [19], in terms of administration, effect and risk profile. The clinical outcomes could have an effect on patients' health and daily life [36]. Currently, there is no clear evidence on which treatment is greater for all patients. Therefore, by assessing preferences of patients with rheumatoid arthritis, there is great potential to provide relevant information for regulatory marketing authorisation decisions [37, 38].

Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory autoimmune disease, characterised by painful inflammation of the joints and fatigue. The prevalence varies by population, with approximately 0.8% in Sweden [39]. It is important to find a suitable treatment as soon as possible, as early treatment is associated with better clinical outcomes [40]. If not successfully controlled, patients can experience joint destruction and loss of functional capacity. The disease can also lead to extra-articular manifestations associated with increased mortality [41]. Patients are usually treated with disease-modifying anti-rheumatic drugs (DMARDs) that target inflammation in the joints. There are numerous DMARDs available with different modes of action and practical characteristics, such as method of administration, frequency of administration, risk of adverse events or monitoring requirements [42].

First-line and second-line treatment options

Newly diagnosed patients with rheumatoid arthritis usually start their treatment with conventional synthetics (csDMARDs) as first-line standard treatment. When standard treatment is not effective or tolerated by patients, treatment is typically changed to biological (bDMARDs) or JAK-inhibitors (tsDMARDs) targeting specific biological mechanisms associated with the initiation and progression of inflammation. Changes from treatment with biologics to JAK-inhibitors or vice-versa may also occur, often due to inefficiency of the first medical product or side effects [42].

JAK-inhibitors are a new class of DMARDs. They work by blocking a cellular signalling pathway inside the cells. Older biologics block inflammation from outside of cells. When approving JAK-inhibitors, the European Medicines Agency took into account the lack of treatment options for patients with rheumatoid arthritis and the fact that JAK-inhibitors can be administered orally instead of subcutaneous injection or intravenous infusion, making it convenient for patients [9]. Current information on the relative importance of treatment attributes is important since the effectiveness and risks of side effects of the recently introduced JAK-inhibitors are not fully defined, in particular in relation to long-term use in an everyday practice.

Second-line treatments have the potential to be more effective than first-line, because they target specific parts of the immune system to reduce inflammations. However, the risk of getting a serious side effect is higher for second-line treatments [9]. Many patients with rheumatoid arthritis are not effectively treated with second-line DMARD treatment (biologics or JAK-inhibitors). The under treatment may be due to inadequate information to support treatment decisions. One of the most difficult decisions for patients with rheumatoid arthritis is whether to change treatment if their current treatment is not effective enough [43].

Patients in research

There may be several reasons why patients are being invited to provide their input in health research. Acknowledging the patient perspective in research has the potential to improve the quality of the research by strengthening the methodological and research outcomes, making it more realistic and patient-centred [44]. There is also an ethical reason for patients to be invited to participate in health research. If research results are expected to have an impact on the patients' health, they should be part of that research [45].

There is an important distinction between the different levels of patient input using the following three terms: *involvement* is when people are actively involved in research projects and in research organisations. *Participation* is when people take part in a research study. *Engagemen*t is when information and knowledge about research are shared with the public [46]. For the involvement to be successful, patients in research should have an active and equal role throughout the whole project [45].

Patients in this thesis

Patients were invited as interviewees (research subjects) in studies II, III and IV. Research partners (i.e. patients from the Swedish Rheumatism Association that have received education to be part of research projects) were invited in studies III and IV. The aim of including patient research partners was to improve the research and make it more patient-centred and targeted to the patient needs. Initially, patients were not involved in the writing of the project plan. The research questions and study design were decided upon by the research team when developing the research plan.

Interviewees

Patients were 'interviewees' in study II as respondents in individual interviews (n=5) with the objective to get a first insight into patient knowledge and needs regarding assessments of patient preferences to inform regulatory marketing authorisation decisions. That information was used to generate an interview guide (pilot tested in n=2 patients) for focus group discussions among patients with rheumatoid arthritis (N=18). Respondents in the focus groups supported the research by exploring patient perspectives on the value of having patient preferences in regulatory decisions. The findings were taken into account for the development of the patient preference study and the educational tool.

Research partners

The patient research partners were recruited via the Swedish Rheumatism Association. The research partners were involved in several steps of the research process (Table 1).

Table 1. Research partners in studies III and IV

Research process	Research partners
Identifying and prioritising	Validating meetings to identify patients' relevant attributes and levels
Commissioning	Validating meeting for framing of the patient information and survey information
Designing and managing	Recruitment strategies, content and design of the educational tool
Undertaking	Pilot-test of the survey and educational tool
Dissemination	Analysis and dissemination of results
Implementing	Promote use of results
Evaluating impact	Developing frameworks for involving patients in other research projects

In *identifying and prioritising*, the patient research partners supported the identifying, selecting and framing of the attributes and levels for the preference assessment as members in validation meetings. The attribute selection was also influenced by three focus groups with patients (n=7). *Commissioning* was assessed in the identification of information needs and framing of the information throughout the educational material to ensure the right content and phrasing. All of the decisions along the *design and managing* stages were discussed among the research partners, such as the images and pictograms. Preliminary pilot-testing of the survey was *undertaken* among patients (n=4) in 'think aloud' interviews. Additionally, the survey and the educational tool were pilot-tested among (n=22) patients. The results of the interviews were discussed among the research partners to improve comprehension of the survey. The research partners made significant changes to the preference assessment before launching the survey by contributing to the final framing of information and attributes and attribute levels. The research partners were involved in the *dissemination* by supporting the interpretation of the findings from the analysis and provided input in the discussion of the results. Minutes were kept to *evaluate impact* of all meetings using a protocol for developing future frameworks for involving patients in upcoming projects.

The input of patients throughout studies II, III and IV is illustrated in figure 3.

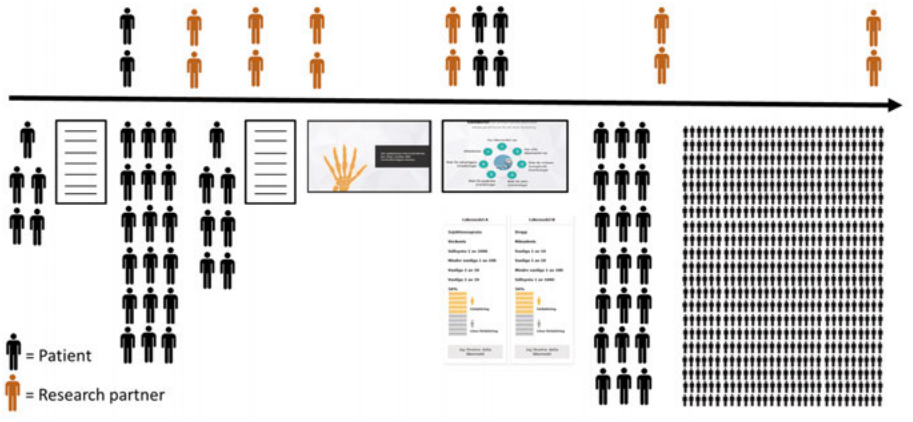

Figure 3. Patients in the thesis (studies II, III and IV).

PREFER

This research is part of the European public-private partnership PREFER ('Patient Preferences in Benefit and Risk Assessments during the Drug Life Cycle'), launched in 2016. PREFER is a 5-year project, funded by Innovative Medicines Initiative 2 (IMI; Europe's largest public-private initiative aiming to help the development of better and safer medicines). IMI is a joint venture of the European Commission and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations [3].

PREFER aims to strengthen patient-centric decision-making throughout the medical product lifecycle with development of evidence-based recommendations on how and when patient preference studies should be performed, as well as how the results of these patient preference studies can be used to inform decision-making processes along the medical product lifecycle. These recommendations will guide the different stakeholders (pharmaceutical industry, regulatory authorisation agencies, health technology assessment bodies, reimbursement agencies, academics, healthcare professionals, patients and patient organisations) on how and when to conduct patient preference studies and to use the results.

Rationale

The use of patient preference information in the regulatory marketing authorisation process may be important for different reasons. It could provide decision-makers and health professionals with additional information to align decisions with preferences of the end-users. It may lead to regulators making more acceptable decisions, and might therefore improve treatment compliance and progression of disease management for patients.

The inclusion of patient preferences in regulatory marketing authorisation decisions is currently hindered by the lack of guidance on when and how to assess patient preferences and how to use this information. Patient preference studies need to be tailored to the regulatory context in order to provide useful information in an understandable and accurate form to inform regulatory marketing authorisation decisions. Attributes relevant for regulatory marketing authorisations may be difficult for patients to understand, such as potential risks and their probabilities. Despite this challenge, there are no or only a few recommendations to guide researchers in educating respondents and assessing their preferences.

Additional best-practice patient preference studies are critically needed to support the development of a structured approach for how and when to assess patient preferences and to use the results in the regulatory marketing authorisation process for the benefit of patients.

Aims

The overall aim of this thesis was to explore how patient preference information may be relevant for regulatory marketing authorisation decisions.

Specific aims were:

I To 1) identify the decision-making processes and decision-points throughout the medical product lifecycle for industry, regulatory authorities, and reimbursement/health technology assessment bodies, and 2) determine which decision-points can potentially include patient preference information.

II To explore how patients with rheumatoid arthritis value the use of patient preference information in regulatory decision-making regarding medical products.

III To assess preferences regarding second-line treatments and heterogeneity within these preferences for patients with rheumatoid arthritis.

IV To determine the influence of an educational tool, compared with traditional written information on patient preferences elicited in a discrete choice experiment.

Methods

Design

The studies in this thesis include qualitative exploration, qualitative patient preference exploration, and quantitative patient preference elicitation. An overview of the methods in this research project is presented in Table 2.

Table 2. Overview of methods

Article	Approach	Data collection	Study sample	Analysis
I	Qualitative explorative	Validation meetings Semi-structured interviews	Representatives: Industry n=24 Regulatory n=23 HTA bodies n=23	Framework analysis
II	Qualitative explorative	Semi-structured interviews Focus groups	RA patients n=18	Content analysis
III	Qualitative preference exploration Quantitative preference elicitation	Nominal group technique Discrete choice experiment	RA patients: n=358	Descriptive statistics Multinomial logit Latent class analysis Relative importance Minimum acceptable benefit
IV	Quantitative preference elicitation Educational tool	Discrete choice experiment	RA patients: Written information n=358 Educational tool n=317	Descriptive statistics Multinomial logit Random parameter logit Relative importance

Article I: An overview of critical decision-points in the medical product lifecycle: Where to include patient preference information in the decision-making process?

The main goal of this study was to identify critical decision points throughout the medical product lifecycle with the potential to include patient preference information. We also wanted to find the activities carried out during the decision points, the types of assessments made at these points, and the assessment criteria used to make decisions at these points separately for the pharmaceutical industry, regulatory marketing authorisation agencies and reimbursement agencies/health technology assessment bodies.

A decision was defined as 'a judgment, conclusion or determination reached after consideration'. We defined a critical decision point as an 'identified fixed moment within the decision-making process along the medical product life cycle where a decision is taken that influences the course of the medical product or device development, authorisation or reimbursement'. A four-step approach was applied in designing this study, including step 1) scoping literature review, step 3) semi-structured interviews, and steps 2 & 4) validation meetings.

Scoping literature review

The literature search was performed to identify relevant white and grey literature [8]. The literature was retrieved via five scientific databases. We searched the databases for relevant titles and abstracts published. Inclusion criteria included: conceptual or applied descriptions of decisions made by industry or regulatory authorisation agencies or reimbursement/ health technology assessment bodies related to medical products; and the use of patient preferences in decision-making by industry or regulatory authorisation agencies or reimbursement/health technology assessment bodies regarding medical products. Articles were excluded when not written in English, no full text available, published before 2011, and country outside of the United States/European Union.

Semi-structured interviews

The semi-structured interviews included respondents representing the stakeholder groups (industry, regulatory agencies and health technology assessment bodies/reimbursement agencies), recruited via purposive sampling and snowballing. The interviews were conducted in Sweden, UK, Italy, the Netherlands, France, Germany, Romania and the US.

The interview guide was based on the emerging topics from the literature review. In total, 72 interviews were planned, four interviews with every stakeholder group in the main countries and two interviews per stakeholder group in the validation countries. Ultimately, the final number of interviews was dependent on data saturation. The interviews were conducted by five researchers via telephone or face-to-face and took approximately one hour. All interviews were conducted in English, audio recorded, transcribed and analysed through framework analysis [9] using NVivo software [10].

Framework analysis

The framework analysis is a qualitative method to organise data in multi-disciplinary health research teams. This method was chosen because of the potential to support teams of multiple researchers, when not all members have experience of qualitative data analysis. There were specific steps to be followed using this method, which produced structured outputs of summarised data [47]. The framework analysis was initiated by transcribing and coding of the interviews. Thereafter, the framework was developed based on the conduct and analysis of the interviews. Fragments of text from the transcribed interviews were coded as a first step. Codes were then categorised and summarised.

Validation meetings

Validation meetings with representatives from each stakeholder group were conducted to validate the results from both the literature review and the semi-structured interviews. The first round of meetings with each stakeholder group was conducted after the literature review to confirm the identified decision-making processes. The second round of meetings took place after the semi-structured interviews to discuss the results of the interviews.

Article II. Patient Perspectives on the Value of Patient Preference Information in Regulatory Decision-Making: A Qualitative Study in Swedish Patients with Rheumatoid Arthritis

This study aimed to explore how patients value the use of patient preference information in the regulatory marketing authorisation process. A 2-step approach was applied with a pilot of semi-structured interviews with representatives from regulatory marketing authorisation agencies and patients with rheumatoid arthritis, followed by focus groups with patients in Stockholm and Uppsala, Sweden.

Semi-structured interviews with regulators and patients

Interviews were conducted individually with regulatory decision-makers (n=4) from the Swedish Medical Products Agency regarding their opinions on the value of patient preferences in regulatory decision-making. Patients with rheumatoid arthritis (n=5) were also interviewed individually to gather preliminary insights on knowledge and opinions on the use of patient preferences in decisions in the regulatory marketing authorisation process. Patients' were eligible if aged 18–80 years old, established diagnosis of rheumatoid arthritis, within different stages of treatment, or representing a patient organisation. Patients were asked to participate in the interviews by their rheumatologist. The interviews were audio-recorded, transcribed verbatim and analysed using qualitative content analysis [48]. Sub-categories and main categories generated themes which were used to develop an interview guide for the main study with focus groups.

Focus groups

Four focus group discussions with patients having rheumatoid arthritis were conducted to explore the patients' perspectives on the value of patient preferences in regulatory marketing authorisation decisions. Patients were purposively sampled via the Rheumatism Association in Stockholm and Uppsala, Sweden. Inclusion criterion were: 18–80 years of age, established diagnosis of rheumatoid arthritis and different stages of treatment. A total of four focus group discussions were conducted with 3–6 participants in each group (n=18). Each focus group lasted ~120 minutes. All focus group discussions were audio-recorded and transcribed verbatim. A qualitative content analysis with a manifest and inductive approach was applied to analyse the discussions [48].

Article III: Patient preferences on rheumatoid arthritis second-line treatment: A discrete choice experiment of Swedish patients

Finding a suitable second-line treatment for patients with rheumatoid arthritis can be challenging. Usually, patients try different medical products in order to find a suitable treatment. This is a situation in which multiple treatment alternatives exist, and there is no option that is clearly superior for all patients. Biologics and JAK-inhibitors have different administration methods that may influence the patients' preference. The patient population is a diverse group at different disease stages, ages, different experiences of side effects and the effectiveness of a medical product. Therefore, a 2-step approach was applied to assess patient preferences on second-line treatment for patients with rheumatoid arthritis. In the first step, attributes and levels were identified for the discrete choice experiment. The second step included the design and the survey.

Discrete choice experiments

We assessed treatment preferences of patients with rheumatoid arthritis using a discrete choice experiment. A discrete choice experiment, a cross-sectional survey method, was used to assess preferences because it allows for quantification of patient preferences for healthcare policies, services and interventions [49]. This method can also be used to measure and explain heterogeneity within the preferences of patients [23]. Discrete choice experiments aim to quantify the relative importance of one treatment characteristic over another treatment characteristic. Respondents are presented with hypothetical choice questions with varying attributes and levels. Participants are assumed to choose their preferred option for each question [50]. The utility is estimated by modelling the respondents' choices between competing treatment alternatives [22].

Recruitment

An advertisement inviting members of the Swedish Rheumatism Association to participate in the study was shared via email, newspaper, newsletter, social media, mobile application and the association's website. The invitation was also distributed to patients attending ten rheumatology clinics in Sweden and via an online research panel. A printed copy of the survey was distributed by the Rheumatology clinic at Uppsala University hospital. Patients were included when: established RA diagnosis, 18–80 years of age and the ability to understand and answer the questions in Swedish.

Attributes and levels

Attributes and levels for the discrete choice experiment were identified through a scoping literature review, validation meetings and focus group discussions. The scoping literature review resulted in 12 potential treatment attributes [34, 51-59]. The potential attributes were discussed with a rheumatologist to make sure that they reflected current clinical practice. Focus groups discussions were conducted using the nominal group technique with patients having rheumatoid arthritis (n=7); these patients were asked to identify new attributes and rank potential attributes from most to least important [60]. Results from the focus groups were discussed during several validation meetings, including one rheumatologist, the research team, and two patient research partners. These meetings resulted in the attributes: route of administration, frequency of use, probability of mild short-term side effects, probability of side effects changing appearance, probability of psychological side effects, probability of severe side effects, and effectiveness of treatment. Each attribute was described using three levels, based on current clinical knowledge of existing second line treatment of rheumatoid arthritis with biologics and JAK inhibitors. All attributes and levels included in the survey are displayed in Table 3.

Table 3. Attributes and levels

Attributes	Levels
Route of administration	
	Tablet
	Injection
	Drip
Frequency of use	
	Daily
	Weekly
	Monthly
Risk of mild short-term side effects: nausea, vomiting or headache	
	Common: 1 of 10 gets the side effect
	Uncommon: 1 of 100 gets the side effect
	Rare: 1 of 1000 gets the side effect
Risk of external side effects: hair loss, weight gain or rash	
	Common: 1 of 10 gets the side effect
	Uncommon: 1 of 100 gets the side effect
	Rare: 1 of 1000 gets the side effect
Risk of psychological side effects: anxiety, mood changes, depression or sleep disturbances	
	Common 1 of 10 gets the side effect
	Uncommon 1 of 100 gets the side effect
	Rare 1 of 1000 gets the side effect
Risk of severe side effects that require hospitalisation: severe infections or allergic reactions	
	Common: 1 of 10 gets the side effect
	Uncommon: 1 of 100 gets the side effect
	Rare: 1 of 1000 gets the side effect
Effectiveness: the ability to decrease inflammation and swelling of the joints, also pain and other symptoms	
	30% Chance of improvement
	50% Chance of improvement
	70% Chance of improvement

Design

The discrete choice experiment had an attribute-based experimental design. Respondents were presented with 15 hypothetical questions, where each included two different treatment alternatives.

Experimental design

Experimental design refers to how attributes and levels are combined into alternatives and choice questions. The experimental design is a systematic plan that ensures that the pattern of choices provides sufficient statistical material to estimate choice-model parameters. The *d*-efficiency is a measure to compare the relative efficiency of an experimental design with another [61].

Pilot design

Attribute and level combinations for the pilot study were determined by a *d*-efficient experimental design using the software NGene 1.0 (ChoiceMetrics, 2011). The survey was pilot tested among a convenience sample (n=22) of patients with rheumatoid arthritis. Six of the pilot-tests were 'think aloud' interviews with patients. The participants were encouraged to express their thoughts, which came up during completion of the survey. The interviews were conducted to evaluate the information and explanation of the attributes and levels and the clarity of the questionnaire design.

Main design

The experimental design for the main survey excluded illogical combinations of attribute levels and also defined several combinations that condition each other (e.g. route of administration 'tablet' and frequency of use 'monthly'). Initially, an optimal design required a large number of choice questions, which is demanding for participants. Therefore, a blocked design was chosen to divide the choice questions equally across the population for the main survey. The blocked design decreases the number of choice questions for each participant, thus lessening the burden for the participants and strengthening the validity of the results [61]. The final experimental design comprised 60 choices, which were divided into four blocks of fifteen choices. The respondents received the following decision-making scenario 'Think of a situation where your treatment is not working, your joints are swollen, you have pain or unbearable side effects, and you need to change to a second-line treatment'. Figure 4 provides an example of a choice question.

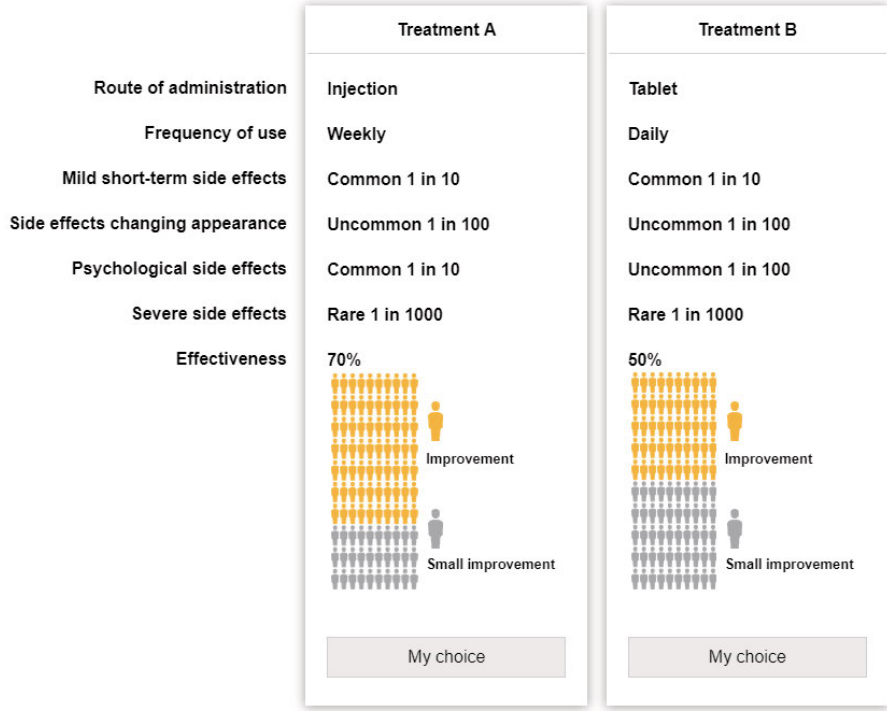

Figure 4. Example of a choice question

Statistical analysis

Demographic data were analysed using descriptive statistics. Results were considered statistically significant if $P<0.05$. Latent class analysis models were used to analyse the data. Such models account for the multi-level structure of the data (i.e. every respondent answered multiple-choice questions) and account for the investigation of preference heterogeneity. Latent class models assume that there are two or more latent classes of data with different preferences. The classes are characterised by unobserved latent variables that can be related to a set of choice patterns. Once choice patterns have been stratified into classes, it is possible to use the model to determine the probability that a participant with certain characteristics will be assigned to each class [62]. The 'likelihood ratio test', the Akaike information criterion (AIC) was used to determine the most appropriate model.

Several demographic and disease-related variables were tested for their potential impact on class membership in the latent class analysis: age, gender, numeracy, health literacy, education level, disease duration, occupational status, and experience with treatment and side effects. To determine the relative importance of the attributes, we calculated the difference between the highest and lowest estimates of the attribute level for each attribute. The largest difference value was given a 1, representing the attribute that was deemed most important by respondents. The other difference values were divided by the largest difference value, resulting in a relative distance between all other attributes and the most important attribute.

We calculated the minimum acceptable benefit from changes in attribute levels. Minimum acceptable benefit is interpreted as the minimum change in effectiveness that respondents would require (on average) to accept changes to a less desirable level in another attribute (probability of getting a certain side effect by 10%, 1% and 0.1%). Minimum acceptable benefit was estimated as the difference between the preference's weights (parameters) for two levels of an attribute divided by the preference weight.

Article IV: Does being exposed to an educational tool influence patient preferences? The influence of an educational tool on patient preferences assessed by a discrete choice experiment

This article is based on the same discrete choice experiment as in article III, designed to assess patient preference regarding second-line treatment and heterogeneity within these preferences, for patients with rheumatoid arthritis living in Sweden. We designed an educational tool to support respondents in the discrete choice experiment to evaluate the risks and benefits associated with hypothetical treatment options for second-line treatment of rheumatoid arthritis.

Recruitment and respondents

Recruitment of respondents started in November 2018 and ended in October 2019. Patients were recruited via three sources: a research panel (n=162) (dynata.com); the Swedish Rheumatism Association (n=228); and rheumatology clinics in Sweden (n=283). Respondents were eligible if they had established diagnosis of rheumatoid arthritis, were between 18–80 years old, and could understand and answer the questions in Swedish.

Study design

The attributes and levels for the discrete choice experiment were identified in a stepwise manner following established methodological standards [18] via a literature overview, validation meetings and focus group discussions with patients. A preliminary list of attributes and attribute levels drafted from the literature overview was revised based on feedback from the validation meetings and the focus group discussions. Seven attributes were included in the DCE: route of administration, frequency of use, probability of mild short-term side effects, probability of side effects changing appearance, probability of psychological side effects, probability of severe side effects, and treatment effectiveness.

Development of the educational tool

All respondents of the discrete choice experiment received the same training content in one of two forms: either as a written (plain) text or as an educational tool. The training content and the educational tool were developed in parallel with the choice questions. The research team created the (written) content of the educational tool; thereafter, the company *MindBytes* developed a multimedia, digital version using text, voice-over, illustrations, graphics, click-on functions, pictograms and icon arrays. *MindBytes* is a Belgian company that applies a theory-driven and evidence-based approach to developing interactive gamified educational tools (http://www.mindbytes.be), helped with the development of the educational tool, including the illustrations.

We began with an overview of the literature pertaining to anti-rheumatic drugs to describe the disease context and the attributes and attribute levels included in the choice questions. Two rheumatologists, two patient research partners and the team of researchers reviewed the first draft. Thereafter, the research team met a second time to review the changes made in response to the first round of comments.

Based on the study population's information needs, a high level of realism and a moderate interactivity level were incorporated in developing the tool. Both the plain (written text) and enhanced versions (educational tool) contained the same information. The attribute levels for the educational tool were given as text, voice-over, illustrations and images. Pictographs were used to describe risks and percentages. Icon arrays were used to illustrate effectiveness (i.e. 1 in 10). The framing of rheumatoid arthritis and the description of the attribute levels were slightly changed based on respondents' feedback from a pilot test of the discrete choice experiment and the educational tool.

Experimental design

The experimental design generated by NGene 1.0 (ChoiceMetrics, 2011), provided each respondent with 15 hypothetical choice questions, with two alternatives characterised by varying the attribute levels. The discrete choice experiment was a forced choice experiment with no opt-out provision.

Statistical analysis

Demographic questions were included in the survey to describe the study population. These related to age, gender, educational level, occupational status and rheumatoid arthritis. Specific questions referred to the disease duration, personal experience of side effects, time to onset of drug effect, and experience with treatment. Measures of health literacy [63] and subjective numeracy [64] were also included to compare the two research arms. Questions regarding the participants' understanding of the background information and the difficulty of the questionnaire were included to determine whether the different formats of educational materials had any impact on their ability to make choices.

Patient preferences were determined by attribute level estimates and the relative importance of the attributes. The attribute levels were estimated using a multinomial logit model [65]. The scale parameter test by Swait and Louviere was used to assess whether there were any differences in the level of error variance (choice consistency) in the two data sets (i.e. those who received the educational tool and the plain text) [65].

A random parameter logit model was used to estimate heterogeneity in preferences. Estimates of random parameters are viewed as average values associated with a standard deviation, describing the heterogeneity of preferences within the sample. Estimates of attribute level indicate the more preferred outcome as a higher estimate. The model included all attribute levels for the choice questions. All attribute levels were tested for interaction with the educational tool. The parameter estimates for the interaction terms can be interpreted as preference-weight adjustments that apply only to respondents in the corresponding subgroup (educational tool).

Relative importance scores were calculated based on results of the random parameter logit models separately for the plain text and the educational tool. The difference between the highest and lowest estimates of the attribute level was calculated for each attribute. The largest difference value was assigned a 1, representing the most important attribute. The other difference values were divided by the largest difference value, revealing the relative distance between all other attributes and the most important attribute.

Summary of results

Article I: An overview of critical decision-points in the medical product lifecycle: Where to include patient preference information in the decision-making process?

A total of 15 critical decision points were identified within the medical product lifecycle with the potential to include patient preference information. Six decision points were identified for industry decision-making. Three decisions points were identified for the regulatory marketing authorisation decision-making. Six decision points were identified for health technology assessment bodies/reimbursement agencies' decision-making.

There was a general agreement among all stakeholder groups that patient preference information may be relevant when making decisions along the medical product lifecycle. A condensed overview of all critical decision points for each of the stakeholder groups is illustrated in Figure 5.

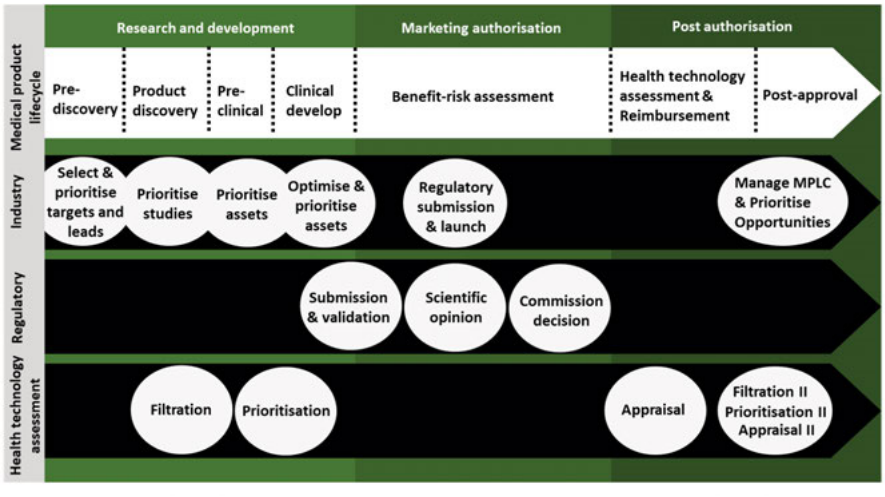

Figure 5. Decision points in the medical product lifecycle

Research and Development

Select & prioritise targets and leads (industry) is based on biology data from human and animal disease pathology overlaps. The decision is based on animal efficacy and toxicity, pharmacology, pharmacokinetics, and drug metabolism characterised. *Prioritise studies (Phase 1) (industry)* is the decision on whether to enter clinical development, peer-reviewed by committees that verify safety, quality, regulatory documentation and resource availability. The decision to continue clinical development is based on pre-clinical performance, literature data, manufacturing data, operational feasibility and verification.

Prioritise assets (Phase 2) (industry) is a decision on whether to enter Phase 2 of clinical development. The decision is based on healthy volunteers or patients to identify the target product profile. *Filtration (health technology assessment/reimbursement)* narrows down prospective assessment topics to a manageable number for investigation. Medical products that are not deemed relevant to health technology assessment are removed by applying pre-established criteria in an implicit or formal process. *Optimise & prioritise assets (Phase 3) (industry)* determines whether to enter Phase 3 of clinical development. *Prioritisation (health technology assessment/reimbursement)* determines the significance of the filtered technologies according to their relative importance and deciding which will be invested in assessment resources. *Submission & launch (industry)* is the decision to evaluate efficacy and safety to support a favourable medical benefit-risk profile and planned label claims.

The semi-structured interviews with industry representatives revealed a positive perspective towards using patient preference information, especially in early stages of the medical product lifecycle. It was suggested that companies are better at informing and communicating their research and decisions when engaging patients.

Marketing Authorisation

Representatives from regulatory agencies identified three situations in the regulatory marketing authorisation process to include patient preference information. *Submission and validation* is when a pharmaceutical company submits an application for a marketing authorisation of a medical product. *Scientific opinion* is a positive or negative recommendation based on a scientific evaluation, on whether to authorise a medical product or not. *Commission decision* grants, refuses, changes, suspends or revokes marketing authorisation.

Regulatory representatives also expressed a limited acceptance for patient preference information and that there is a need for a structured way to include such information in decisions. One respondent said, '*All these things are very important but you have to create a way of measuring the impact of taking into account patient preference'*. Another one said, '*For me, it would be the ideal world if you have your - you will have a preference model of almost every disease, and you can use this preference model with every new drug to see how it fits into what will be the overall benefit risk assessment'*. Others expressed that patient preferences information could be more important in specific situations. '*I think that for marketing authorisation decision, usually patient preference or patient input can maybe change the decision a little bit when the benefit-risk ratio is borderline or not really defined in a rare disease. And for this rare disease when you have no other option, it is important to have input from patient preference'*.

One of the regulators specifically expressed the need for patient preference information in decisions relating to rare diseases. '*I think the situation where we need patient input is, one thing when we have very rare diseases. Because I think, I mean, if I look at the CHMP we are, a lot of us are doctors. I think we know a lot about the clinical practice; I think we can make quite a lot of decisions that will benefit patients. We can be rather sure that I think; what I am trying to say is that we really have the patient first. But when it comes to very rare diseases, there it can be difficult for us to judge if we see treatment effect of a product. It may be statistically significant compared to what you compare to, placebo whatever it is. But, we may have difficulty to understand if this effect is of clinical relevance or not. That is much easier to understand if it's a common disease where we have maybe seen it a lot, but if it's very rare disease, we've never seen a patient with this disease, then it's very difficult, and then it's very helpful to get the patient's input on; do you think this effect would be of use for you?*'

Post-Authorisation

Appraisal (health technology assessment /reimbursement) reviews the materials and evidence assembled during the assessment step by the health technology assessment body. Manage medical product lifecycle & prioritise opportunities (industry) may be enhanced to further satisfy unmet medical needs. Filtration II, prioritisation II and appraisal II (health technology assessment/reimbursement) are the reassessment processes when market conditions change, or there is new evidence indicating changes in safety or action mechanisms. Steps are repeated, but they incorporate new evidence and document clinical effectiveness and/or cost-effectiveness.

Representatives from health technology assessment bodies/reimbursement agencies had a positive perspective towards the use of patient preference information, since the current patient involvement mostly consists of one patient, which might not carry much weight in decision-making. Industry representatives discussed that patient preference information is valuable for dossiers to regulators and for health technology assessment/reimbursement to provide context and conclusions around the datasets.

Article II. Patient Perspectives on the Value of Patient Preference Information in Regulatory Decision-Making: A Qualitative Study in Swedish Patients with Rheumatoid Arthritis

Most respondents in the focus group were female (n=17) within the age range of 28-79 years (mean 59) and highly educated (n=8). The time since diagnosed with rheumatoid arthritis varied from 1-42 years.

Value of patient preferences in regulatory decision-making

Respondents in the focus groups discussed the patients' *right to influence regulatory decisions* and that patient preference information may give them the opportunity for such involvement. They also believed it was important for regulators to consider patient preferences, because they may consider potential benefits and risks differently. Respondents also said that patient preferences could inform regulatory decision-makers on valuable characteristics of treatment to fit patients' needs, lifestyles and well-being.

Some concerns were raised in the focus groups on conducting patient preference studies. One was patients' limited knowledge regarding medical products, which could result in an incorrect view of what patients really prefer. Another concern related to the ways in which patients with rheumatoid arthritis are different. Specifically, they have different disease trajectories, symptoms and treatments; they may respond to treatment differently and experience varying side effects. Lastly, they may differ in their preferences.

Informing regulatory marketing authorisation decisions by assessments of patient preferences may be especially important for patients with rheumatoid arthritis because it is a chronic condition with high prevalence. Respondents also addressed that patients might have greater knowledge in what would fit patients' needs, lifestyles and well-being, compared with the knowledge of regulatory decision-makers. Respondents identified steps in the medical product lifecycle for the use of patient preferences. Some respondents said that it may be of greatest importance in early development of medical products in order to design patient-friendly products. However, all of the focus groups discussed that patient preferences should be incorporated into the marketing authorisation processes when evaluating potential risks and benefits against each other.

Some respondents expressed a concern regarding pharmaceutical companies conducting preference studies. According to them, pharmaceutical companies lie to patients because they only care about profit. When discussing their perspectives on experiences with disease and treatment, some respondents said that in order to have and express a preference, there is a need to include patients with experience to some extent. The respondents also expressed a need for patients to be informed about the use of their preferences in the regulatory process. They also desired to have information about rheumatoid arthritis and the medical products before they could participate in a preference study. Most of the respondents preferred to have written information and questionnaires as opposed to interviews because it gives them time to think about their answers. Online surveys might be suitable for patients since they allow for more flexible interaction, also convenient for patients with rheumatoid arthritis since it can be difficult to write with a pen.

Article III: Patient preferences on rheumatoid arthritis second-line treatment: A discrete choice experiment of Swedish patients

In total, 358 patients were included in the analysis. Most of the respondents were female (77%), between 18–80 years of age and highly educated (45%).

On average, the multinomial logit model revealed that most of the respondents preferred taking a tablet instead of an injection or drip. Respondents also preferred having monthly medication rather than weekly or daily. A strong disutility was found for the highest frequency of side effects in all of the three classes. Finally, respondents preferred the medicine with the highest effectiveness. The latent class analysis revealed that the most important attributes for respondents were the probability of severe side effects, treatment effectiveness and route of administration (Table 4).

Table 4. Preferences of patients based on latent class analysis

		Class 1 Estimate	SE	Class 2 Estimate	SE	Class 3 Estimate	SE
Route of administration							
	Tablet	1.22***	0.27	0.92***	0.20	1.14***	0.19
	Injection	0.37**	0.17	0.51***	0.15	0.64***	0.16
	Drip (ref)						
Frequency of use							
	1 a day	-1.00***	0.18	-0.75***	0.16	-0.59***	0.14
	1 a week	-0.47***	0.17	-0.23	0.14	-0.02	0.16
	1 a month (ref)						
Probability of mild short-term side effects							
	1 in 10	-0.30*	0.17	-0.27*	0.14	-0.44**	0.17
	1 in 100	-0.15	0.13	-0.08	0.12	-0.06	0.14
	1 in 1000 (ref)						
Probability of side effects changing appearance							
	1 in 10	-0.87***	0.20	-0.34**	0.16	-1.55***	0.21
	1 in 100	-0.04	0.17	-0.10	0.14	-0.48***	0.15
	1 in 1000 (ref)						
Probability of psychological side effects							
	1 in 10	-1.11***	0.23	-0.75***	0.18	-2.61***	0.28
	1 in 100	-0.01	0.18	-0.62***	0.15	-0.34**	0.17
	1 in 1000 (ref)						
Probability of severe side effects							
	1 in 10	-1.75***	0.27	-0.21	0.18	-3.65***	0.39
	1 in 100	-0.82***	0.16	-0.08	0.12	-0.79***	0.16
	1 in 1000 (ref)						
Effectiveness (linear)		0.12***	0.01	0.01**	0.00	0.04***	0.00
Class probability model							
Constant		1.32	0.96	2.51***	0.96	-	-
Disease duration		-0.16	0.12	-0.32***	0.12	-	-
Experience with mild side effects		-0.46	0.36	-0.99**	0.39	-	-
Average class probability		0.34		0.28		0.38	

Note: ***, **, and * significance at 1%, 5% and 10%, respectively.

Relative importance

We calculated the relative importance scores of the attributes separately for the three classes of the latent class analysis (figure 6). Respondents in class 1 found treatment effectiveness to be the most important attribute, class 2 respondents found the route of administration to be the most important attribute, and class 3 respondents found the probability of getting severe side effects as the most important attribute. Respondents with newly-diagnosed rheumatoid arthritis and no experiences of mild short-term side effects were more likely to belong to class 2, whereas respondents with longer disease duration and previous experience of mild short-term side effects were more likely to belong to class 3.

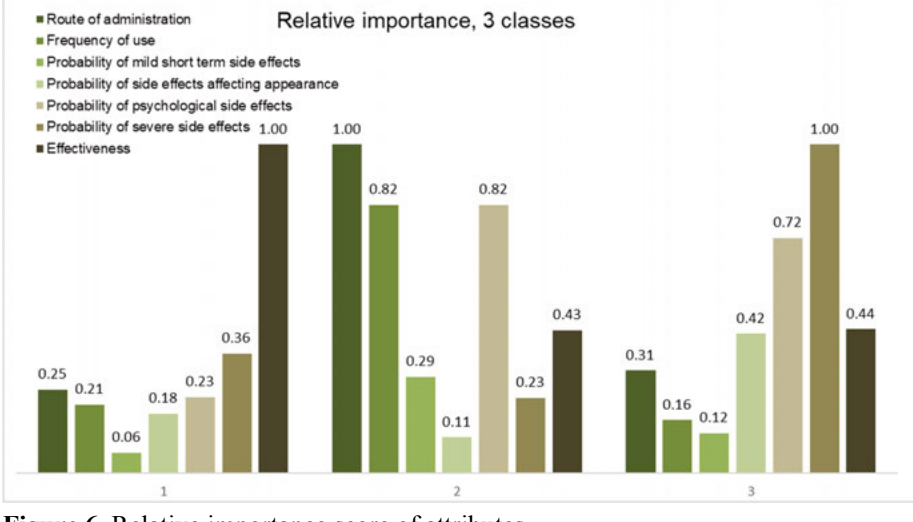

Figure 6. Relative importance score of attributes

Minimum acceptable benefit

The minimum acceptable benefit levels required (in percentage point increases in effectiveness) to compensate respondents for worsening levels of probability of certain side effects are presented in table 5. We found large differences across the three classes. In class 1, only a small benefit was needed to accept a switch to a less favourable frequency of side effects. In the other two classes, respondents would require a larger increase in effectiveness to accept an increase in risk of side effects. The highest levels were seen in class 3 respondents for moving from a 0.1% probability of getting a severe side effect to a 10% probability, which required a 91.3 percentage point increase in treatment effectiveness. The second highest level was seen in class 2 for moving from a 0.1% probability of psychological side effects to a 10% probability, which required a 75.0 percentage point increase in treatment effectiveness.

Table 5. Minimum acceptable benefit for changes in attribute levels

Attribute	**Change**	**Minimum acceptable benefit in percentage**		
		Class 1	Class 2	Class 3
Probability of mild short-term side effects				
	Moving from 0.1% to 10%	2.5	27.0	11.0
	Moving from 0.1% to 1%	1.3	-	1.5
	Moving from 1% to 10%	1.3	35.0	9.5
Probability of side effects changing appearance				
	Moving from 0.1% to 10%	7.3	34.1	38.8
	Moving from 0.1% to 1%	-	10.0	12.0
	Moving from 1% to 10%	7.6	24.0	26.8
Probability of psychological side effects				
	Moving from 0.1% to 10%	9.3	75.0	65.3
	Moving from 0.1% to 1%	-	62.0	8.5
	Moving from 1% to 10%	9.3	13.0	56.8
Probability of severe side effects				
	Moving from 0.1% to 10%	14.6	21.0	91.3
	Moving from 0.1% to 1%	-	8.0	18.8
	Moving from 1% to 10%	21.4	13.0	71.5

Note: - no significant estimate

Article IV: Does being exposed to an educational tool influence patient preferences? The influence of an educational tool on patient preferences assessed by a discrete choice experiment

In total, 675 patients with rheumatoid arthritis were included in the analysis, where 358 received the training material in plain written text and 317 received the training material as a web-based educational tool. The majority of the respondents were female (80%) and highly educated (47%). The same percentage worked full-time (43%) as were retired or unemployed (43%). The average time for completing the full survey was 18 minutes for respondents using the plain text and 27 minutes for respondents using the educational tool. All attributes significantly influenced decision-making, with most showing significant standard deviation (SD) for heterogeneity. Patients' preferences depended on the training material (i.e. plain text and educational tool) (table 6.)

Table 6. Preferences of patients based on random parameter logit model

Attribute	Plain text*		Education tool*	
	Estimate	SD	Estimate	SD
Route of administration				
Tablet	1.45***	0.91***	1.12***	0.70***
Injection	0.73***	0.86***	0.44***	0.69***
Drip (ref)				
Frequency of use				
1 a day	-1.04***	0.60***	-0.28***	0.84***
1 a week	-0.39***	0.10	-0.13	0.04
1 a month (ref)				
Probability of mild short-term side effects				
1 in 10	-0.46***	0.05	-0.73***	0.01
1 in 100	-0.07	0.35***	-0.78***	0.27
1 in 1000 (ref)				
Probability of side effects changing appearance				
1 in 10	-1.02***	0.13	-1.13***	0.07
1 in 100	-0.22**	0.07	-0.08	0.22
1 in 1000 (ref)				
Probability of psychological side effects				
1 in 10	-1.63***	1.05***	-2.02***	0.88***
1 in 100	-0.43***	0.18	-0.57***	0.01
1 in 1000 (ref)				
Probability of severe side effects				
1 in 10	-2.18***	1.12***	-2.58***	1.34***
1 in 100	-0.58***	0.07	-0.68***	0.06
1 in 1000 (ref)				
Effectiveness (linear)	0.07***	0.05***	0.06***	0.03***

Note: * see manuscript for SE and SD,
***, ** significance at 1% and 5%, respectively.

Relative importance

The relative importance scores revealed that respondents receiving the educational tool placed relatively more importance on the probabilities of all side effects than respondents receiving the plain text version. The probability of getting a severe side effect was most important for those receiving the educational tool. Treatment effectiveness was most important for respondents receiving the plain text information. Both groups had similar preferences for third place (probability of getting a psychological side effect), fourth place (route of administration), and fifth place (probability of getting a side effect changing appearance). Least important were frequency of use and the probability of mild short-term side effects (figure 7).

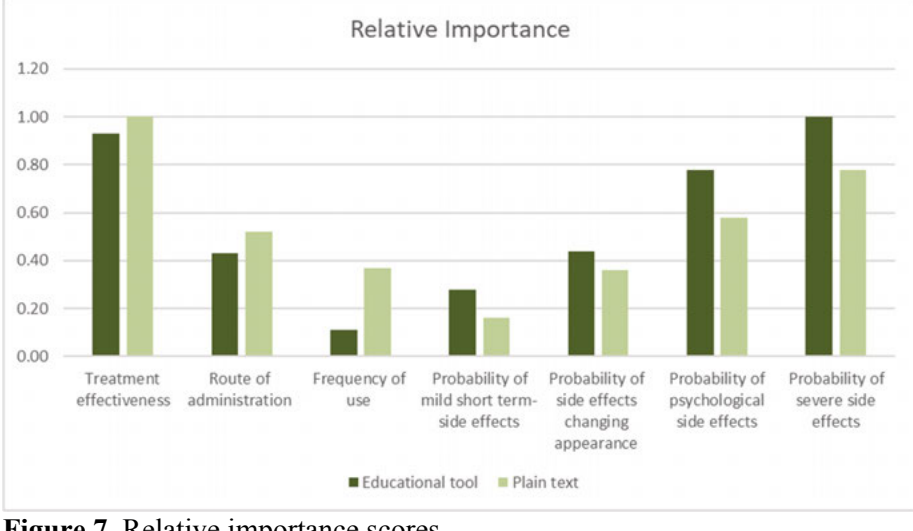

Figure 7. Relative importance scores

Discussion

Key findings

The aim of this thesis was to explore how patient preference information may be relevant to regulatory marketing authorisation decisions. Therefore, this thesis started by identifying decision processes along the medical product lifecycle with the potential *decision points* where to include patient preference information. Three decision points were identified for regulatory marketing authorisation decision-making (submission and validation, scientific opinion, and commission decision) in which patient preferences were considered as being relevant information by the regulators. Despite the potential of integrating patient preferences at numerous stages, various barriers may prevent the inclusion of patient preferences [66]. Some of the barriers may relate to concerns among stakeholders regarding the validity of the preference study [30]. To this end, it is not clear which stakeholder should conduct the preference study, how to inform the respondents, how to deal with preference heterogeneity, and how much weight patient preference information should be given in a decision.

Regarding the implementation of patient preference studies, the initiative usually comes from either the pharmaceutical company applying for marketing approval or from the patient advocates. However, such approaches can make it difficult for decision-makers to take the information into account, as it may not be tailored to the regulatory context. A more stakeholder-oriented approach may be more suitable to close this gap. This can be done by focusing on collaborations among the end-users of patient preference information, such as the pharmaceutical industry, regulatory agencies, health technology assessment bodies/reimbursement agencies, patients and physicians in order to make the study relevant to the specific decisions and disease contexts.

Patients were interviewed to get their perspectives on the use of patient preferences in marketing authorisations (study II) [67]. An important finding from that study was the underlined importance of being properly informed when answering a preference study. This finding mirrors the stakeholders' concerns regarding the need for patients to be informed [29, 66]. Existing guidance also emphasises the need for patients to be 'well-informed', by means of being able

to cognitively process and understand the health outcomes, associated benefits, risks and uncertainties [10]. Properly informing respondents on benefits and risks in a preference study may potentially increase the validity of the result. A valid result may potentially increase the weight given to the patient preference information. Therefore, respondents of study IV were given the educational material in two different forms to assess if the format of the educational material influenced their choices, which it did, at least to a small extent. Patient preferences differed depending on whether respondents received educational material in the form of plain text or as an educational tool (i.e. using text, voiceover, illustrations, images, pictograms, icon arrays and click-on functions). Respondents receiving the educational tool placed relatively more importance on all the probabilities of all side effects compared to those receiving the same content in plain text. It is possible that informing respondents using an educational tool might be more efficient when the decision context is not previously well known to the respondents, as in this study, approximately half of the respondents had had their disease for more than 10 years.

The preference assessment in study III was also designed to be relevant for regulator marketing authorisations by revealing heterogeneity in patient preferences assessed by a discrete choice experiment. This study revealed substantial preference heterogeneity among patients with rheumatoid arthritis. Respondents mainly focused on three things: the probability of getting a severe side effect, effectiveness of the treatment, or the route of administration. A sub-group of patients with higher acceptance of severe side effects was also discovered (i.e. the effectiveness group) [68]. Such results from a patient preference study may have the potential to support a favourable benefit-risk profile. In some cases, it may be appropriate to approve a medical product for use in a subset of the patient population, for which a warning is needed to inform patients about the side effects. When making such a decision, the regulatory agency may consider patient preferences along with the evidence from clinical and non-clinical testing. These medical products need careful targeting, monitoring and follow-up. Assessments of patient preferences may also be considered as information that can support a refusal of a medical product approval; for example, if the patient reports that the minimum acceptable benefit level of a proposed medical product is lower than the expected outcomes.

Regulatory implications

Regulators have two main tasks; to evaluate the quality of the provided data and the benefit-risk assessment. They mainly base their decisions on pre-approval studies; clinical trials at a population level. One implication of this thesis relevant to regulators is that quantitative assessments of patient preferences can combine patients' value judgements with scientific rigour. Therefore, it has the potential to provide additional information to marketing authorisation decisions; information that is not captured in clinical trials [66].

Information of the relative importance of relevant benefit-risk outcomes and heterogeneity within patients' preferences, and the minimum acceptable benefit may provide essential information to support scientific evaluations for new medical products [68]. Patient preference studies may also be considered in post-approval activities that are carried out as long as a medical product is approved; usually a marketing approval lasts for five years. Post-approval activities include safety monitoring and ongoing benefit-risk assessments. Information regarding preferences for side effects that appear when a medical product is tested in everyday practice could potentially inform a medical product renewal [69]. For a renewal, patient preference information may support scientific evaluations by clarifying and updating on patients' views on side effects that appear after being used in a wider range of the patient population (i.e. people that were not included in the clinical trials) [9].

The semi-structured interviews with representatives from regulatory agencies in articles I revealed that there is no common practice for how to use patient preference information. Sometimes, their agency receive such information in the submission and validation, but they do not know how much weight it should be given in the scientific evaluation and opinion [66, 67]. However, the weighting process may simultaneously consider the patient preference information on relevant benefit and risk outcomes, their likelihoods and impact on the patient [70]. Therefore, a structured approach to assess patient preferences is needed to qualify patient preference information as valid scientific evidence for regulatory marketing authorisations [10]. Article III and IV add to the qualification of patient preference information by quantifying and communicating patients' views on what matters most to them. Article III revealed that there was a sub-group of patients willing to accept higher risks of severe side effects in order to gain a possible benefit, compared to the rest of the respondents [68]. Regulators might consider such a sub-group in the scientific evaluation and opinion. Article IV showed that the ways attributes are presented to patients significantly impacts patients' preferences. Therefore, regulators should carefully consider the information format when receiving patient preference studies.

Transferability of the results

The results of this thesis may also be transferable to other countries, stakeholders and diseases.

To other countries

A pharmaceutical company can apply for marketing approval via the centralised authorisation procedure of the European Medicines Agency that covers medical products in all Member States of the European Union. Alternatively, an application can be made via a national marketing authorisation procedure working closely with the European Medicines Agency. The research in this thesis was mainly conducted in Sweden, so relevant questions might be is this thesis only relevant to the Swedish context? Or can the results be transferable to all member states of the European Union?

The focus of the first study in this thesis was the European stakeholder perspective on the potential to have patient preference information in decisions along the medical product lifecycle. The interviews were conducted in Sweden, the United Kingdom, Italy, the Netherlands, France, Germany and Romania. However, interviews were also conducted in the United States. Therefore, these results may potentially be transferable to other similar countries. The second study focused on the Swedish patient's perspective on the value of having patient preference information in regulatory marketing authorisation decisions. This study may not be transferable to other European countries, as attitudes may differ across countries, including also the trust in national authorities, which may differ across countries.

Results from the patient preference study reveal that a significant number of patients in Sweden found effectiveness of treatment to be the most important and that they would accept an increased risk of side effects for an increase in effectiveness. The results may not be generalisable to other European countries, as the healthcare systems are different. For example, in Sweden, the disease modifying anti-rheumatic drugs are reimbursed for patients with rheumatoid arthritis by the government. People may also have varying views on benefits and risks in different countries. However, there is some concordance between the results of similar, previous, studies from numerous countries [71]. Transferability of the results may be ensured by replicating the study in other countries and comparing the results.

To other stakeholders

The regulatory marketing authorisation process was the context of this thesis. Nevertheless, the results might also be relevant to other stakeholders of the medical product lifecycle, such as industry, health technology assessment bodies/reimbursement agencies, physicians and patients. Patient preferences may support the pharmaceutical industry by revealing the minimum acceptable benefit required in order to accept an increase in chances of getting a certain side effect. Information on patient values that might support the pharmaceutical company's application to a regulatory agency. Health Technology Assessment bodies allocate healthcare resources by assessing the costs and benefits of health interventions [72, 73]. This research also has the potential to inform the decision on whether to reimburse an authorised medical product by presenting the relative importance of treatment characteristics. Specifically, this research provides an overview of differences in treatment preferences. Such results may lead to more accurate and acceptable marketing authorisation decisions that may improve the progression of disease management. The results may also be transferable to physicians and patients in discussions on considering benefits and risks of possible treatment alternatives.

To other disease areas

The results of this thesis may not be transferable to other diseases, but lessons learned from the research process may be applicable to preference research in other disease areas. This thesis has provided knowledge related to selection and framing of attributes, involving patient research partners; identification of information needs and the development of educational materials; pre-testing of the preference study; and recruitment of respondents. Moreover, it has presented results in a form that may be relevant to end-users of the patient preferences.

Methodological considerations

This thesis contributes to the methodological discussions on how to make patient preference studies relevant to regulatory marketing authorisations. A strength of this thesis is the use of both qualitative and quantitative methods to answer different research questions. Qualitative exploration was used to assess the stakeholders' and patients' perspectives in studies I and II. Studies III and IV were initiated by qualitative preference exploration in identifying attributes for the discrete choice experiment. Quantitative preference elicitation was used to assess stated preferences of patients with rheumatoid arthritis. However, there are methodological considerations and limitations of all studies in this thesis that need to be discussed.

Article I

The first study of this thesis included a comprehensive methodological approach with a scoping literature review, semi-structured interviews of representatives from regulatory marketing authorisation agencies, health technology assessment bodies/reimbursement agencies and pharmaceutical companies, and validation interviews. The number of interviewees (n=70) from different countries captured a unique international perspective. It was possible to create a novel and highly representative overview of the decision-making processes and the potential for including patient preferences in the medical product lifecycle, which has not previously been outlined. However, the perspectives of patients and other stakeholders are also important in the successful use and integration of patient preference information.

Article II

Trustworthiness is a key challenge in qualitative research. Another important challenge is to clarify who is heard, the respondents or the researchers' interpretation, when reporting the results [74]. There are three components used to obtain trustworthiness: creditability, transferability and dependability. To obtain credibility, it is crucial to recruit respondents with some knowledge. The description of the context of the study is important for the transferability of the study findings. Therefore, we started with the semi-structured interviews to identify the current knowledge and information needed to be able to talk about the use of patient preferences in regulatory marketing authorisations. The semi-structured interviews revealed that patient preference studies and the regulatory marketing authorisation process was not well known. To obtain dependability, two researchers independently identified the codes and categories in the analysis, and all of the authors were involved in summarising the results.

Articles III and IV

Measurement validity captures whether the results from a discrete choice experiment meet face, content, convergent and external validity. The concepts are used to assess the accuracy of the instrument for measuring preferences and to determine how generalisable the preferences are in other circumstances [75]. When measuring face validity, the extent to which the results are consistent with priori expectations is assessed. Face validity can be assessed by considering how the results match 'intuition'. Results of the discrete choice experiment revealed that all of the beta values were in the expected direction (i.e. positive for effectiveness and negative for side effects).

Content validity relies on the extent to which the discrete choice experiment accounts for things that are important in the construct's domain. This relates to the attributes and levels in a discrete choice experiment [75]. For this research, experts and research partners were consulted, and pilot tests were conducted to obtain content validity. Convergent validity measures the extent to which the results are consistent with other measures to measure the same construct. Convert validity can be obtained by comparing results of a discrete choice experiment, for the same treatment from the same population regardless of the method used [75]. The results from this research add to previous research by applying patient preference elicitation methods to patients with rheumatoid arthritis to the regulatory context [19]. External validity refers to the extent to which the results can be generalised to situations and people outside the study. One way to do this is by studying real world choices and revealed preferences and comparing to the preferences in this research. This may be also done by jointly estimating revealed and stated-preference estimates [75]. A possible limitation with this research may be the lack of external validity. However, observed preference heterogeneity has been reported to correctly predict >93 percent of choices in discrete choice experiments [76].

Measurements of reliability captures if the discrete choice experiment produces similar results under constant conditions. Preference reliability includes concepts of consistency and holdout tasks. It measures whether results can be reproduced or repeated over a given time. Measurement reliability will never be perfect in any situation because of simple variation in responses [75]. Testing consistency of respondents' answers can be obtained by different indication measurements. The effect of cognitive ability on preference formation and understanding of the survey instrument (cognitive tasks) was assessed by examining the relationship between psychological constructs of cognitive ability (health literacy and numeracy) and survey responses. This included a comparison of response times for completing the survey and attitudinal questions about reported complexity in the choice questions and the perceptions of

the educational material. A suggestion for further research may be to include comprehension tests to compare educational tools to plain text [77].

Ethical considerations

All procedures performed in the studies involved human participants and were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was granted for all of the studies included in this thesis by the Regional Ethics Review Board in Uppsala, Sweden. Informed consent was obtained from all individual participants included.

Respondents of the semi-structured interviews in studies I and II were asked to answer questions about their views on the use of patient preferences in regulatory marketing authorisation decisions. Additionally, patients in study II were asked demographic questions relating to health that may be viewed as sensitive to the respondent. The patients in study II were invited to the study via their rheumatologist or the Swedish Rheumatism Association. Patients in studies III and IV received information via the Rheumatism Association, a research panel or clinic. All the respondents received an information letter from a third party and could decide to sign up for the interviews or the preference study themselves. The information letter informed about the aim of the study, how the study would be conducted and how the data would be managed. All respondents provided their informed consent after being given the opportunity to ask questions to the researchers.

Having patients influencing regulatory marketing authorisation decisions acknowledges the patients' right to have a say in decisions affecting their health. The use of patient preferences may be seen as something that is good in itself, as it recognises patients' values as equal to the values of the regulators. It can also be good because of what it brings, such as better decisions in line with patients' preferences. When getting a say, it is also important to give patients an opportunity to express preferences that are both informed and reflected. Therefore, the educational material was designed with the intention to support the respondents in evaluating potential treatment-related benefits and risks to make an informed decision that more accurately reflects real life preferences.

To receive or not receive an educational tool may be understood as something that has consequences for respondents in a patient preference study. A patient who finds it important to be part of a medical product approval decision might feel it is empowering to be able to provide an informed preference. Patients may also feel that educational tools are a form of paternalism by correcting or manipulating the information given. In the first view, informing patients' preferences by an educational tool has intrinsic value by recognising patients as worthy in making medical decisions.

Patients as research partners

The main reason for including patient research partners in this thesis was to improve the research by making it more patient-centred. A limitation of the inclusion may be that the initial plan did not include a plan for patient input. However, a strength may be that the recruitment of research partners was supported by the Swedish Rheumatism Association. The association already had a structure to prepare patients to become a research partner. Another limitation may be the lack of good practice for evaluating the process. Therefore, a protocol was developed among the research team. The aim of the protocol was to capture the research partner perspective, in terms of the 'feeling of being involved' and the 'actual changes made to the research'. Working with research partners benefited the research, as the patient perspective was not well-known to the research team. However, there is a need for more research to gain examples of best practices on how to evaluate the effects of patient input and recommendations to support researchers in including patients.

Practical implications

This research contributes to fill the current gap in methods to assess patient preferences and to present the results in a form that may be relevant for decision-makers in the regulatory marketing authorisation process. The input from patients in the research process and as respondents in interviews and the preference assessment may have gained the acceptance and relevance of the research. As methods to inform respondents of patient preference studies are under-reported, the development and assessment of the educational tool may provide input for future patient preference studies.

This thesis is also an attempt to change the attitudes among stakeholders of the medical product lifecycle. Assessments of patient preferences make it possible to include a representative sample of patients in the decisions. The health of patients and their quality of life may depend on whether or not a medical product is approved. Information gained by this thesis on preference heterogeneity and the minimum acceptable benefit may guide future research and regulatory marketing authorisations in giving patients a say on what matters most to them. Patients may be more understanding of their treatment if they accept the potential side effects and the practical characteristics of the prescribed medical product. Additionally, this thesis contributes to the development of a structured approach for the use of patient preferences in decisions along the medical product lifecycle.

Future research

There is a need for specific recommendations to improve collaborations among stakeholders in order to achieve a more stakeholder-oriented approach when conducting patient preference studies and integrating patient preference information in decisions along the medical product lifecycle. Nevertheless, there is still uncertainty regarding how educational materials influence patients' preferences. There is a need for guidance on how and when to develop educational materials in order to strengthen the validity of patient preferences in assessments. Therefore, future research may consider the recruitment of respondents that are less knowledgeable on the disease and the medical products. An additional suggestion for further research is to develop universal guidance on comprehension tests for preference research to be able to assess comprehension among respondents. Research including patients should also consider the involvement of patients throughout the research. Therefore, there is a need to gain more knowledge on how to involve patients in research and how to evaluate the effects.

Conclusions

Patient preference information may be relevant to regulatory marketing authorisation decisions by providing additional information in the form of patient values. This may improve decision-making by making it more patient-centred. Quantitative assessment of patient preferences, conducted by discrete choice experiments is a promising way to identify patient preferences; the relative importance of different treatment characteristics, heterogeneity within patients' preferences and the minimum acceptable benefit. A condition for the use of patient preference information in marketing authorisations should be that the patients have understood the attributes and levels. Therefore, it is important to tailor educational materials to the patients' cognitive ability and information needs. Guidelines for when and how to measure patient preferences needs to be developed to enhance the inclusion in actual decision making.

Sammanfattning

Myndigheter som bestämmer om nya läkemedel ska godkännas vet mycket om läkemedelssäkerhet. Men inte lika mycket patienternas perspektiv och preferenser. Ibland bjuds patientrepresentanter in för att föra patienternas talan i beslutsprocesserna, men det är svårt för *en* representant att representera *alla* patienter. Därför har vi undersökt hur man på ett systematiskt sätt kan ta reda på hur patienter väger risk mot nytta och hur den informationen kan komma till nytta för myndigheter när de ska fatta beslut om vilka läkemedel som godkänns och inte.

Det övergripande syftet med den här avhandlingen är att ta reda på hur beslutsfattarna ska kunna väga in patienters preferenser i beslut om att godkänna, eller inte godkänna, ett läkemedel. Tillsammans har jag själv, mina handledare och forskare i ett stort europeiskt forskningsprogram vid namn PREFER undersökt en metod för att undersöka patienters preferenser. Metoden är kvantitativ och kallas för ett *Discrete Choice Experiment*. Där får deltagare, i det här fallet personer med ledgångsreumatism, välja mellan två hypotetiska behandlingsalternativ genom att väga nytta mot risk. Valsituationen upprepas och när tillräckligt många val har gjorts kan man utläsa ett mönster. Det mönstret visar patientens preferenser.

Ett av målen med avhandlingen har varit att se om patienter och beslutsfattare accepterar information från sådana preferensstudier som underlag för beslutsfattande. Resultaten visar att både beslutsfattare och patienter var positiva till att använda preferensstudier i beslutsprocessen, men att deltagarna i preferensstudien behöver tillräcklig information för att fatta informerade beslut. Ett annat mål med avhandlingen har varit att ta reda på hur personer med ledgångsreumatism faktiskt väger risk mot nytta med andra linjens läkemedel mot varandra. Resultaten visar att det finns tre tydliga preferensmönster bland studiens deltagare. Några vill ha en effektiv behandling och fokuserar inte så mycket på biverkningarna, andra ansåg att sättet som läkemedlet tas på var viktigast och den tredje gruppen vill absolut inte ta ett läkemedel med allvarliga biverkningar.

En viktig del av en preferensstudie är att deltagarna får information om valen de kommer att ställas inför. Den här informationen kan presenteras på olika sätt. För att se om sättet informationen presenteras på skulle göra att deltagarna svarade på olika sätt använde vi två olika metoder. Hälften av deltagarna fick skriftlig information om nytta och risker hos läkemedel. Den andra hälften fick informationen genom ett digitalt utbildningsverktyg där den presenterades i text, med röstinspelning, bilder, interaktiva inslag och ikoner. Efter att alla deltagare svarat gick det att se en skillnad. De som fick informationen genom det digitala utbildningsverktyget fokuserade mer på biverkningar medan de som fick skriftlig information fokuserade mer på effektivitet.

Sammanfattningsvis finns en stor potential för att använda preferensstudier som underlag för beslut om att godkänna eller inte godkänna läkemedel. För att kunna göra det krävs att personerna som deltar i studien ska ha tillräckligt med information och tillräcklig möjlighet att reflektera kring risker.

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