MASTER THESIS

Patient involvement in benefit-risk assessment at the European Medicines Agency

A patient-informed analysis to determine the room for improvement by using quantitative patient preferences

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Content

Abstract

Objectives The European Medicines Agency is Europe's regulatory authority for the market approval of drugs based on formal assessment of benefits and risks. Patients are increasingly involved in these assessments through their presence in appraisal committees. The aim of this study is to assess the possible value of stated preference methods in addition to current ways of patient involvement in the approval decisions by providing benefit and risk trade-offs from a patient perspective.

Methods A document analysis was conducted to analyse the current ways and level of patient involvement in benefit-risk assessment. Second, an online questionnaire was used to assess the possible use and value of stated preference methods in representing the patient perspective in benefit-risk assessment. The questionnaire was send to 159 patients who have been involved in EMA activities during the year 2012.

Results A total of 45 documents were thoroughly analyzed. The findings show that the current level of patient involvement in benefit-risk assessment is low. There are a number of barriers for patient involvement, such as the ad-hoc nature of patient consultations and the absence of a right to vote for patients. Thirty-seven (23%) out of 159 patients completed the questionnaire. Stated preference methods are not being used yet, but according to the patients stated preference methods could be used in benefit-risk assessment, in particular to increase the transparency of how the patient perspective in regulatory decisions is used.

Conclusion From this study it appeared that current patient involvement in benefit-risk assessment at the EMA can be improved. While in the current benefit-risk assessments quantitative patient preferences are not considered, patients regard them as a future way of pursuing this improvement and achieving objectives of patient involvement. If patient preferences are used, several measures are however needed to facilitate their use. For the future, studies should take a broader focus considering stated preference methods one method available to involve patients.

1. Introduction

1.1 Benefit-risk assessment at the EMA

In the European Union the European Medicines Agency (EMA) is the regulatory authority responsible for market approval decisions of new drugs [1]. Based on Directive 2001/83/EC, the quality, safety and efficacy of medicines should be at a sufficient level to gain market access [2]. Approval shall be refused if ''(a) the risk-benefit balance is not considered to be favourable; or (b) its therapeutic efficacy is insufficiently substantiated by the applicant; or (c) its qualitative and quantitative composition is not as declared'' [3].

At the EMA, the Committee for Medicinal Products for Human Use (CHMP) is responsible for medicines intended for human use and is supported by working parties (WP's) and scientific advisory groups (SAG's). Benefit risk assessment (BRA) is the complex process of balancing the benefits and risks. However, benefit and risk are evaluative terms. Determining whether a consequence of taking a drug is positive or negative and the extent to which this is the case, involves value judgements [1]. Secondly, benefit and risk have different dimensions. Risk is a probability, i.e. the likelihood of the occurrence of a particular unfavourable effect, while benefit is a quantity, the good of a product or magnitude of loss averted [1]. Comparing these is like comparing apples with oranges. To overcome the variability in interpretation of risks and benefits, the EMA has recently proposed the use of favourable and unfavourable effects as part of their benefit-risk methodology project. Given the difficulties of BRA, the goal of that project was to assess possibilities for a qualitative or quantitative structuration of the assessments [4, 5].

Another issue in benefit risk assessment is the perspective from which the evaluation is made. While it is the patient that is the ultimate beneficiary (or victim) of access to the drug, experts panels that consist of e.g. pharmacologists, doctors and biochemists, make the decisions in the assessments. It is likely that these regulators and patients think differently of what constitutes a favourable or unfavourable effect and how it would impact their life [1, 6, 7]. In recent years authorities have focused on involving patients and their perspectives in the assessments.

1.2 Patient involvement

There are several reasons to involve patients in benefit risk assessment. Two fundamental objectives can be distinguished. First, patients should be involved for democratic reasons, i.e. democratic principles suggest that the ones affected by a decision should also be involved. Associated means objectives are that involvement promotes transparency, validity, legitimacy, and it increases the fairness of the process [8-10]. Although patient involvement per se does not automatically result in these. It can for instance be imagined that for an increase in transparency the results of patient involvement have to be published [11]. Second, patient involvement is needed for instrumental reasons, i.e. to better inform decisions [10]. Means objectives are that patients provide valuable experiential knowledge about living with a condition and the (un)intended consequences of a drug, and the quality of the decision increases as the decisions better reflect patients' values and preferences. Also, patients can provide an additional and different perspective on what are perceived to be acceptable benefits and risks [1]. This helps balancing the views of different stakeholders [9, 10, 12].

To achieve objectives of patient involvement, patients can be involved at different levels. A useful distinction can be made between communication, consultation and participation. In communication patients are informed by the organisation about topics deemed relevant to the patient by the organisation. During consultation patients are invited to comment on topics issued by the organisation. Participation is about an exchange of information that allows both parties to suggest new topics [13].

On these different levels, patient involvement can be operationalized in two ways. The first way is direct involvement, where patients are directly involved in the decision making process, e.g. by involvement in a committee or advisory group [14]. Examples of direct involvement on the level of communication are informative reports and a website. Consultation examples are a focus group or online consultation and examples of participation are a citizens' jury or meetings which include voting rights for patients [8, 9, 12].

The second way of patient involvement is through indirect involvement for which a distinction can be made between qualitative techniques [9] and quantitative techniques [12]. Quantitative methods elicit a patients' preference for alternative options while comparing multiple attributes like benefit and risk-profiles [7, 9], or possibly other characteristics like process factors (e.g. interaction with the physician) and personal factors (e.g. health history) [7, 15, 16]. The patient's value ''for a specific component or attribute, either in absolute terms or in relation to another attribute'' is measured [16]. Preference elicitation can be considered a form of consultation for BRA [13]. For measuring (quantitative) patient preferences, stated preference methods have to be distinguished from revealed preferences. Stated preference methods present respondents with hypothetical choices for eliciting preferences while revealed preference methods look at the actual choices of individuals [16, 17]. For stated preference methods there are two main categories. Conjoint analysis or discrete choice experiments and multiple-criteria decision analysis (MCDA) usually are methods that provide a relative weight or marginal utility for a given set of attributes. Contingent valuation methods, including willingness-to-pay studies, typically measure the monetary value of an intervention [16-20].

In theory, there are multiple benefits to the use of quantitative patient preferences over direct involvement. From a democratic perspective, representativeness might increase as larger samples are used than is usually the case when directly involving patients. Problems like unclarity about who to involve and the absence of adequate representation can be avoided [8, 17, 19]. Preferences might also take away some of the tension between the 'hard' clinical evidence and 'softer' patient considerations usually expressed by direct involvement [8, 21]. From the instrumental perspective, quantifying patient preferences facilitates direct comparisons for drug-approval decisions. Patient preferences can be compared with actual clinical evidence on benefits and risks, and with risk tolerance among regulators [7]. Patient preferences can also be used to weigh clinical evidence [7]. Finally, it can help patients manage the complex information in assessments [21]. Besides advantages, there are possible drawbacks, both related to the use as the measurement of preferences. Interesting regarding the first is for instance that there are still reservations about the relevance of patient opinions in medical assessments [22]. For other possible problems and drawbacks, and progress made on these issues, reference is made to other sources as they mainly relate to the measurement of preferences [1, 16-19, 23, 24].

In recent years, the EMA has focused on ''empowering patients'' [25]. Patient involvement has grown considerable the past years, shown by the number of patients and activities [26]. According to the EMA, involvement gives the public more trust, confidence and reassurance in the outcomes, and increases the level of transparency. Ultimately, it contributes to the quality of the decisions, it enriches regulatory decisions, and patients provide a crucial patient perspective to the scientific discussions [26-28]. While overall patient involvement at the EMA has grown, the degree of involvement specifically in BRA is not clear. Current attempts to increase patient involvement at the EMA include the development of a new framework on interaction with patients. This framework should include how patients should be involved specifically in BRA and criteria and areas for which consultation or dialogue with patients is needed [26-29]. The framework, in which patients are contributing to its development by means of the Patients' and Consumers' Working Party (PCWP), will be available by the end of 2013 [26, 28, 30].

Although it is not likely that quantitative patient preferences will already be part of this framework, the potential of stated preference methods for measuring and using quantitative patient preferences has not gone unnoticed at the EMA [31]. The EMA for instance performed a study on measuring patient preferences using MCDA [26]. It was suggested that patient preferences could help improve transparency and communication of assessments. One issue that was discussed was what the value of these methods would be to patients. Therefore, in this study the value of stated preference methods/quantitative patient preferences (used interchangeably hereafter) to support patients' voice in BRA was assessed, and where patients believe the use of these methods can contribute to achieving the fundamental and means objectives of patient involvement.

The aim of the present study was twofold. First, the current ways and level of patient involvement in BRA at the EMA were assessed. Second, the perceived value of stated preference methods to patient organisations in addition to the present ways of patient involvement in benefit-risk assessment at the EMA was assessed.

2. Methods

2.1 Data collection

This study comprised a document analysis to evaluate the current level of patient involvement in BRA and a questionnaire to systematically assess if and how to use patient preferences, and what the possible value could be (figure 1).

Document analysis

Overall 45 documents retrieved from the EMA were selected via EMA's website in the period May-June 2013. Three categories of documents were distinguished. Policy documents were to document the current policy on patient involvement (in BRA). Progress documents were used to gather information on policy execution. Drug assessment reports were used to evaluate the extent to which patients have really been involved in assessments, and on which aspects. For the policy documents, a selection was made of documents specifically about patient involvement, documents with a broad focus and therefore likely to include some information on patient involvement and documents on specific EMA organs via which patients can be involved. For the progress documents, reports were

selected that evaluated general patient involvement policy or specific initiatives, and minutes of certain meetings were randomly selected given the large amount of meetings. For the assessments, random selection was used given the large amount of minutes and reports on meetings and decisions regarding assessments.

Questionnaire development

The questionnaire consisted of four different parts. First, previous experiences of respondents regarding involvement at the EMA were categorized to obtain background information. Second, an inventory of relevant aspects regarding the use of stated preference methods led to addressing the questions of when to use patient preferences, who should collect them, in which cases to use them and patients' motivation to personally apply preferences. Answer categories were based on current EMA processes which were identified in the literature search [32-37]. Thirdly, the potential value of stated preference methods according to patients to contribute to objectives of patient involvement was evaluated using acceptance criteria defined by Rowe and Frewer [37] and a decisional conflict scale (SURE scale) developed by Légaré et al [38-40]. Rowe and Frewer's criteria can be classified as democratic reasons for involvement. The SURE scale assesses the uncertainty of patients in decisions, and thus their ability to inform decisions. This is related to the second fundamental objective. For Rowe and Frewer's criteria, items from their own questionnaires were used [41], adapted to the EMA situation. For most criteria only one question was used to keep the questionnaire's length within limits. Fourthly, the need for measures to facilitate using patient preferences was important to assess what more is needed besides patients' willingness to use preferences. The final question addressed options for facilitating patient involvement and the use of patient preferences.

The questionnaire was reviewed by seven patient organisations and in June 2013 it was pilot tested among three PCWP members. This resulted in validation of the criteria used for assessing the value of patient preferences and minor changes in the questions addressing the use of stated preference methods. To further ensure validity of the choice of criteria, an open question was used to assess what respondents consider important for successful patient involvement in BRA [36, 42]. Purposive sampling was used to assure recent knowledge of personal involvement and EMA processes. Those involved in 2012 in EMA activities were surveyed resulting in a sample of 159 patients. These subjects are for reasons of consistency called patients. As results will show they can e.g. be experts (doctors, scientists) or representatives of patient and consumer organisations (PCO's), and at the same time either an actual (former) patient or a non-patient. In all cases they are associated with a PCO. The questionnaire could be finished anonymous and was send in July 2013. Two reminders were sent on weekly intervals. Invitations and reminders were sent via the EMA by an email including the subject and a link to the questionnaire which was administered via Limesurvey. Prior to sending the invitations, the EMA announced the questionnaire during a PCWP meeting.

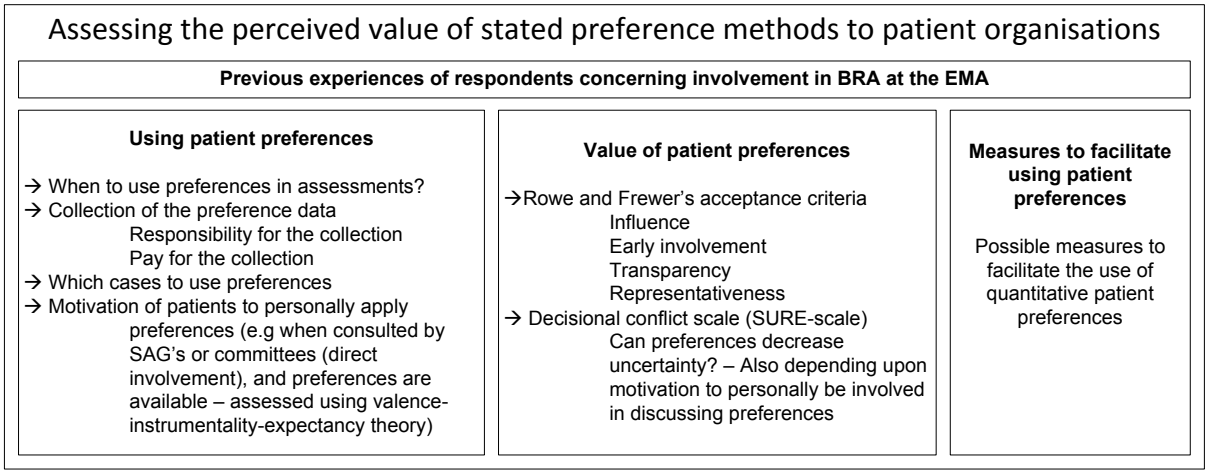

Figure 1: conceptual approach questionnaire

2.2 Data analysis

For the EMA documents a qualitative document analysis was used [43]. A pre-analysis of documents showed limited information on patient involvement in benefit-risk assessment, and when involved, it was difficult to assess whether this related to benefit-risk assessment. Policy, progress and assessment documents were used. For the assessments, the assumption was made that the EMA reports on patients' specific role in a benefit-risk assessment when they have been involved.

Questionnaire data were analyzed using SPSS Statistics version 20. Most data was analyzed descriptively by providing means, standard deviations and frequencies. To measure the added value of patient preferences, the criteria were scored by the respondents for patient involvement in benefit-risk assessment in the current situation, and for a hypothetical situation in which additionally patient preferences would be available. Additionally, since preferences and direct involvement are considered complementary [9, 21, 22]. The difference between the two scores was used as a measure for the added value of preferences on objectives of patient involvement. A non-parametric (Wilcoxon signed rank) test was used to assess the difference. The questions for the criteria are given the use of Likert-scales essentially ordinal variables. Distances between the answer categories were however assumed to be equal allowing calculation of the mean.

3. Results

3.1 Current patient involvement

Document analysis

In the policy documents, the patients' contribution in benefit-risk assessment is regarded important. It is stated that patients enrich regulatory decisions. A new definition on patient involvement in BRA, ultimately leading to patients' utilities being taken into account, should become available as is stated in diverse policy documents. Looking at the actual possibilities for patient involvement in BRA, the number of ways for doing so is low. A limitation for patient involvement is the absence of CHMP membership. Also, consultation by the CHMP seems to be on an ad-hoc basis and not always directly related to the benefit-risk balance [25, 44]. Furthermore, SAG's can provide recommendations on scientific/technical matters for products under evaluation [45], but they do not reflect on the entire

benefit-risk balance. Moreover, they do not directly assess benefit-risk [46], patients have no right to vote, and questions are asked on initiative of the CHMP. Confidentiality agreements apply to the SAG meetings, membership of committees and expert (thus not patient representative) consultation by committees. This means it is not possible for the patients who are involved to consult their members, or communicate issues with their PCO or others. Finally, patients are involved in BRA via the Pharmacovigilance Risk Assessment Committee (PRAC), but this only concerns pharmacovigilance activities and not the entire benefit-risk balance is judged.

Progress documents show that already from the first year (2007) since its launch, EMA's current framework on interaction has been fully implemented and overall involvement has grown [26, 47]. Patient involvement possibly relating to BRA mainly seems to happen via the scientific committees and SAG's. The number of consultations and the issue or drug subject to consultation are often listed. The actual contribution of patients is however unclear. Although matters on which patients were involved sometimes related to benefits and/or risks, they do not directly relate to the judgement of these. The EMA seems to take a 'broad' definition of benefit-risk when talking about patient involvement. For instance, the EMA sees involvement in SAG's as involvement in BRA while this involvement also relates to aspects such as impact on day-to-day life of patients and real life experiences [26, 48]. It is stated in the fifth yearly report on the interaction (describing 2011) that patients can contribute to the discussion on the acceptability of risk. No actual contributions are however reported and no commenting on the benefit-risk balance is seen [26]. Overall, progress documents do show some patient involvement during BRA, but not often, the actual contribution is unclear, and it is mainly on aspects related to the benefit-risk balance and not actual judgement of benefits and risks.

Finally, assessment documents do not show any involvement of patients in the benefit-risk assessments. Report is made that patients have been involved in some related issues. These include for instance consultation on the package leaflet, a paediatric investigation plan, a risk management plan, the European Public Assessment Report (EPAR) format and measures to be taken to minimize the risk of a drug when in use. In the rules of involvement of PCO members in committee related activities (e.g. CHMP or SAG consultations) it is stated that ''if the organisations' representative(s) were consulted on a centralised procedure, this consultation will be reflected in the public assessment report'' [49]. The EPAR summaries and assessment reports however do not show any involvement on the benefit-risk assessment, and only sometimes on related issues.

Questionnaire respondents' involvement

Of the 159 subjects, 37 responded (response rate of 23%). Table 1 provides an overview of the different activities in which the respondents have been involved. A median of two indicates that many respondents have been involved in multiple activities. The actual number of moments they have been involved might even be higher as the patients can participate multiple times in the different activities. Twenty-two respondents, almost 60%, are involved in the management board, one of multiple scientific committees or the PCWP. Most respondents categorize their level of involvement as the highest level of involvement, participation, which was about an exchange of information between the EMA and patients. Of the six who have answered 'other', four indicate all categories, thus including participation.

Table 1 - Descriptives and current involvement of respondents (N = 37)	n (%)
In which of the following EMA activities have you been involved? [A]	
Member of the Management Board	2 (5)
Member of a scientific committee (please specify to COMP, PDCO, PRAC or CAT)	7 (19)
Member of the Patients' and Consumers' Working Party (PCWP)	16 (43)
Member of a certain network (please specify to ENCePP, Enpr-EMa, or another)	2 (5)
Guideline preparation (please specify via which working party)	1 (3)
Product related issues (e.g. SAGs/WPs/scientific committee consultations, participation in meetings) (please specify the activity and the committee, SAG or WP)	14 (38)
Participation in/consultation by specific working groups (please specify the specific working group)	5 (14)
Review of information (e.g. EPAR summaries, package leaflets, safety communications (including training))	19 (51)
Participation in stakeholder meetings relating to the new pharmacovigilance legislation	11 (30)
Conferences/workshops/info sessions organised by the EMA (please specify the activity)	12 (32)
None	1 (3)
Other	3 (8)
In what role did you participate? [A]	
Member (e.g. of the PCWP or a scientific committee)	11 (30)
Representative of a patients' and consumers' organisation	30 (81)
Expert	14 (38)
Observer	8 (22)
Other	2 (5)
What would best describe your overall way of involvement as specified at question 1?	
Communication	1 (3)
Consultation	5 (14)
Participation	23 (62)
Other	6 (16)
Missing	2 (6)
Did or does your involvement, as specified in question 1, allow you to provide input or comment on benefit-risk assessments of the EMA?	
Yes, on the entire benefit-risk balance	10 (27)
Yes, but only on aspects of the benefit-risk balance	10 (27)
No	9 (24)
Do not know	7 (19)
Missing	1 (3)

[A] Respondents were able to select multiple answers; therefore, the total exceeds 100%

Looking specifically at patient involvement in BRA, ten respondents indicated they can provide input on the entire balance. This means they can give their opinion on the relation between benefits and risks. Ten other respondents indicated they can only provide input on aspects of the benefit-risk balance, e.g. on the severity of a particular risk. Comments of this group include that discussion of benefits and risks took for instance place in the Pharmacovigilance Working Party (PhVWP) and Scientific Advice Working Party (SAWP), but this discussion was reduced to less important clinical and technical aspects, was about living with the disease or the patients were only able to vote on leaflets and packaging. Comments from those not allowed to provide input included: ''patients' outcomes are today rarely taken into account in any drug development procedures'' and ''the annual PCWP meeting doesn't refer to actually running evaluation processes''. Finally, the confidentiality agreement needed for involvement in product-related issues (both via committees and SAG's) is considered by some respondents as being a real problem.

3.2 Value of stated preference methods

First, the respondents felt that stated preference methods could be beneficial throughout the process, i.e. from pre-clinical research until pharmacovigilance activities. However, no particular stage seems best for using patient preferences. All stages are supported by between 20% and 50% of the respondents. Secondly, for collecting the preference data EMA is trusted the most (20 out of 37). At the same time the pharmaceutical manufacturer should pay for the collection (21 out of 37). Thirdly, the respondents indicated that preferences can be used in all cases, e.g. high risks and high benefits, except when benefits and the risk for minor adverse effects are low. Nevertheless, not one option has a very high score (all supported by 25% to 50% of the respondents) and quite some respondents (12 out of 37) indicate preferences should always be used. Fourthly, the respondents' motivation to personally play an active role in using preferences was assessed. This personal role can e.g. be relevant when patient preferences are combined with direct involvement. This resulted in a positive but low motivation.

To assess the possible value of patient preferences in relation to objectives of patient involvement the scores in table 2 should be compared to eachother. A one means strongly disagree and a five strongly agree. For the decisional conflict scale, the final score is given as 'DCS total score' which is presented on a four-point scale. For all criteria, except 'early involvement', a higher score is better. Only on the criterion of transparency a significant difference in favour of using patient preferences was observed (W=18, p=0.002). According to the respondents, transparency of the benefit-risk assessments thus increases when patient preferences would be available.

Table 2 - The value of using patient preferences (N = 37)

Criterion	Statement [B]	No preferences mean (SD)	With preferences mean (SD)	P-value
Representativeness	The patient views expressed in BRA are representative of those who are affected by the b/r decisions	3.5 (0.9)	3.6 (0.9)	0.864
Early involvement	Involvement in BRA is taking place too late to allow patients to influence b/r decisions	3.2 (1)	3.2 (0.9)	0.580
Influence 1	Patient views are taken seriously in BRA	3.4 (0.9)	3.5 (1.0)	0.854
Influence 2	Patient views are influential on the b/r decisions made by the EMA	3.3 (0.9)	3.4 (1.0)	0.465
Transparency	It is clear how the results of patient involvement in BRA are used	**2.6 (1)**	**3.1 (1.1)**	**0.002**
Sure of myself (DCS 1)	Patients are sure about the position to take in BRA	3.2 (1.1)	3.4 (1.1)	0.220
Understand information (DCS 2)	Patients are aware of the benefits and risks of a drug when involved in BRA	3.5 (1)	3.6 (1)	0.883
Risk-benefit ratio (DCS 3)	Patients are aware of which benefits and risks are most important to the patient population when involved in BRA	3.8 (0.8)	3.8 (1)	0.658
Encouragement (DCS 4)	Patients have enough support and information to take a position in BRA	3.1 (1.1)	3.4 (1.1)	0.167
DCS total score [C]	Uncertainty surrounding the position to take in BRA	2.4 (0.9)	2.5 (0.9)	0.352

[B] Statements are simplified for data presentation. Full statements can be found in the questionnaire, appendix two

[C] Calculated by converting to a 4 point scale made up of a score between 0 and 1 for each criterion. According to theory, a score less than 3 indicates decisional conflict

Finally, table 3 presents measures needed to facilitate the use of patient preferences. Three groups or levels of measures are identified. According to the first grey group, no additional measures are needed. One respondent indicating that patient preferences cannot contribute did however also indicate that the use of them might be facilitated by easy access to protocols and educating patients on preferences. The white group identifies measures to facilitate the use of patient preferences via different ways of support and increasing patient involvement in general and by direct involvement. While this group of measures might be needed for using patient preferences, they could also merely

serve as facilitating patient involvement in benefit-risk assessment without the use of patient preferences. The second grey group shows measures that might additionally be needed and which relate specifically to patient preferences. Six respondents provided their own answer. These all relate to increasing the level of involvement of patients; knowledge of patients should be taken more seriously, more patients should be involved and more discussion should take place.

Table 3 – Measures needed to facilitate the use of patient preferences (N = 37)	n (%) [A]
Nothing, I do not think quantitative patient preferences could contribute at all in the current benefit-risk assessment processes at the EMA	2 (5)
Nothing, I think the current processes at the EMA offer sufficient possibilities for the use of quantitative patient preferences	1 (3)
Increase the level of involvement of patient representatives regarding benefit-risk assessments of drugs	27 (73)
Assign one or multiple patient representatives to the CHMP	20 (54)
Assign a certain weight to the importance of the patient preferences in assessments	20 (54)
Provision of education and support regarding (the use of) quantitative patient preferences to patient representatives	26 (70)
Provision of education to EMA's scientific committees' decision makers about patients' preferences and real-life experiences	22 (60)
Provision of information on the influence of patient views on decision-making to patient representatives	18 (49)
Provision of easy summaries of assessment reports to patient representatives	21 (57)
A decrease in the technical difficulties (complexity of information in assessment reports) of the assessments for patient representatives	11 (30)
Easy access to key reports/protocols in an assessment for patient representatives	24 (65)
Assign (more) EMA personnel to support patient involvement	17 (46)
Provide more money to patient representatives so they can actively pursue involvement in benefit-risk decisions	20 (54)
Other	2 (6)

[A] Respondents were able to select multiple answers; therefore, the total exceeds 100%

4. Discussion & conclusion

4.1 Discussion

Current patient involvement

The aim of this paper was to study if stated preference methods would be of added value in supporting the patients' voice in BRA. First a document analysis was used to analyse the current ways and level of patient involvement in BRA. Secondly, a questionnaire was used to assess the perceived added value of stated preference methods on criteria of patient involvement.

The results of the document analysis suggest that the current level of patient involvement in BRA is low, despite a SAG pilot phase, a PCWP enlargement and the establishment of the PRAC. Patients are increasingly involved in BRA. There are however barriers that restrict the possibilities to transfer the patient's opinion to the regulators. Comments from the questionnaire's respondents match these findings. When involved, patients cannot directly assess the entire benefit-risk balance. Often the precise contribution of patients is unclear, for instance because of the confidentiality agreement. Further, the assessments do not report patient representatives' contributions, or unwillingness of applicants to consult patients, although both are requested when applicable. It is unclear if this is due to a lack of patient involvement or due to inadequate reporting. In 2007, the EMA stated that the patients' opinion is usually not requested during BRA. Although the document analysis cannot precisely show the change in levels of patient involvement in BRA, the results suggest that

involvement is still low and there is room for improvement considering the advantages of patient involvement in BRA recognized by the EMA.

Most questionnaire respondents indicate their own involvement could be regarded participatory. This is the highest level of involvement as defined by Rowe and Frewer [13]. This contrasts somewhat with the findings of the document analysis. An explanation might be that almost 60% of the respondents are involved in either the management board, one of multiple scientific committees or the PCWP. Considering overall involvement at the EMA [26], the respondents are more intensively involved than other patients. This may lead to selection bias. Therefore, it is believed that the questionnaire results do not alter the previous conclusion about current patient involvement in BRA. This is supported by respondents, of whom some made comments like “the interaction between the EMA and patients and consumers is at an early stage; there is a long way to go on either side”. Another reason why the conclusion does not change is that participatory involvement does not only or necessarily refer to BRA. It also refers to other issues on which patients are involved.

This study’s findings are in agreement with literature. Arnardottir [50] states that the input of patients or their representatives in the CHMP and its organs is purely of an advisory nature, and they are only occasionally invited for consultation. Patients and their representatives are not allowed to participate in the scientific discussions of the CHMP. Furthermore, Mussen states that patient involvement in regulatory decision making at the FDA and EMA ‘’is still often tokenistic and takes little account of the need to present materials in a non-technical way’’ [1].

Overall, there seems to be a gap between the advantages of patient involvement recognized by the EMA, and the actual possibilities for achieving these advantages. As an example, the EMA states that patients provide a crucial perspective to the scientific discussions. Results however suggest that there are barriers to patient involvement limiting the actual possibilities for providing this perspective. Supportive of the fact that the EMA is not yet fully making use of patient involvement in BRA is that for years the EMA is announcing a definition on how patients should become involved in benefit-risk assessment. Since 2009 the need to come with this definition has been mentioned often [26-29, 48, 51, 52], and even recently it is a goal for the PCWP in 2013 [30].

Value of stated preference methods

The most important finding from the questionnaire is that patients believe patient preferences are a possible way for more involvement in BRA. Two aspects need discussion; the height of the scores and the use of quantitative patient preferences.

First of all, considering the scores for assessing the added value of patient preferences, they are already quite high for the current situation. The question is how these scores relate to, based on the document analysis, the current level and room for improving patient involvement in BRA. As with the fact that respondents indicate they are involved in a participatory way, it is not believed that these ‘high’ scores alter the previous conclusion that involvement seems low and that there is room for improvement. One reason for this is again the selection bias of the respondents. A second reason is that the scores on the criteria could relate to those situations in which patients are actually involved (e.g. on particular aspects and not the entire balance) in assessments. When this is the case, the scores can be (quite) high while there is simultaneously room for improving patient involvement.

A second point for discussion is the low perceived added value of patient preferences. The results show that preferences only contribute to transparency. It is believed that patients want to use preferences since their use has value, but that there is not yet value. There are two possible reasons for this. First of all, the current processes might not be suited for using patient preferences. Given current patient involvement in BRA, it could be that it is unclear for patients if, where, how and when patient preferences can be used, and with what effects. For the current processes the respondents gave considerable support to measures relating to the level of patient involvement in BRA at the EMA needed to facilitate the use of patient preferences (white rows – table 3). This included providing information and support to patients, but also increasing the level of patient involvement in BRA. The need for more support is in agreement with what has already been recognized by the EMA [26, 27, 47, 48, 51, 53-55], by patient organisations' research [56] and literature [21, 37]. A consequence of more support could be a decrease in decisional conflict [40], and increasing the level of patient involvement might contribute to a better idea on how to use patient preferences. Although respondents indicated they want more support in BRA and a higher level of involvement to facilitate the use of patient preferences, it is likely that they want these measures anyway. In the reports on interaction with patients it is for instance mentioned that patients seek more involvement in BRA and that they want a CHMP representative [26, 48, 51].

Apart from the current processes, the novelty of patient preferences is a second reason possibly leading to the low added value of patient preferences. As patient preferences are not being used yet at the EMA, patients might not know how to use them. This is illustrated by the fact that preferences should be used at multiple moments and in multiple cases, but not option gets very high support. Another illustration is that, considering the scores on the criteria, the majority scored the current situation equally to a situation in which preferences would be used. To address this problem, respondents supported measures needed to facilitate the use of preferences (2nd grey row – table 3), such as a need for education on preferences. If not only patient involvement in general in BRA has to improve, but also preferences need to be used, these are measures needed according to patients.

The aim of the questionnaire was to analyse the use and perceived added value of patient preferences in BRA. Overall, it can be concluded that patients have a positive attitude towards the use of preferences, but to be of added value several steps have to be taken. In this study it became clear that patients seek measures to increase their involvement in BRA. Interesting for the coming years is whether this will be by direct involvement or by using patient preferences. Since the benefit-risk process at the EMA probably remains qualitative, it seems that when preferences are used, they will act as a guide in the assessments instead of being integrated in a quantitative framework [57-59]. Another development that will influence the possible use of patient preferences is EMA's new definition on patient involvement in BRA. This will affect the alignment between direct involvement and patient preferences. If direct involvement remains low, the need to use patient preferences might increase. Finally, the need for information and support will remain especially useful when patient preferences are not used, since only a number of patients with limited knowledge can be involved [8, 58].

4.2 Future directions

There are several interesting options for future studies. It is important that patient preferences are studied as part of arrangements. Important is whether patient preferences will be part of a qualitative or quantitative process, and how preferences will be aligned with direct ways of

involvement. It would also be wise to include other stakeholders. What do other stakeholders, e.g. methodologists, believe is best for using preferences? Another direction is that similar studies should be done again the coming years. It is not likely that EMA's new policy will already include patient preferences. Once patients are used to this new policy, with perhaps more involvement in benefit-risk assessment, their opinion on preferences might change. Interesting would also be to look at the FDA. At a recent conference they addressed the questions of when to use preferences and who should collect these, of which the results showed some similarities to the results of this study [60]. A reservation to be made regarding these suggestions is that still considerable progress is necessary on the measurement of preferences and the integration of preferences in either qualitative or quantitative frameworks [19, 61].

4.3 Limitations

A first limitation is that an N of 37 has limited the ability to make stronger statements and perform proper subgroup analysis. A second limitation related to the respondents is that while the questionnaire has been send to members of PCO's, given the several activities in which respondents are involved, it is not possible to determine whether they have acted as representative or in their personal capacity, and whether they answered as a patient or non-patient. A third limitation stems from the relatively high level of involvement of the respondents. This might decrease the representativeness as there might be some selection bias. Further, it would be possible to argue that this bias contributed to the low added value of patient preferences (besides the current process and novelty of patient preferences previously discussed), as the respondents scored the current situation already quite high. This cannot be completely ruled out, but is not believed to change the conclusion of this study. First because there is still room for higher scores; they are only high in relation to the level of involvement encountered in the document analysis. Secondly, the relatively high involvement of the respondents stills seems low, meaning also for them added value of using patient preferences was expected.

4.4 Conclusion

The aim of the present study was twofold. First, the current ways of patient involvement in BRA at the EMA were analysed. Second, the added value of quantitative patient preferences in addition to these current ways for achieving objectives of patient involvement was assessed. A thorough document analysis showed that current involvement in benefit-risk assessment can be improved. Although for the current level of involvement almost no potential in stated preference methods is recognized, patients have indicated preferences might be one way of improving patient involvement in diverse stages of BRA. For preferences to be of use, several measures are however needed, including diverse ways of support for patients in BRA and education on patient preferences. While this study focused on patient preferences, the results also point and contribute to a wider movement towards more patient involvement in BRA. Methodological advances regarding stated preference methods are needed, but an interesting future direction this study points to, is to consider patient preferences part of arrangements of patient involvement including both direct and indirect involvement. For the EMA case, the new definition on patient involvement in BRA and the structuration of their assessments will be of influence on these arrangements and the extent to which they help representing patient views and inform the market authorization decisions made.

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Appendix 1: Operationalization questionnaire

The questionnaire consisted of four different parts: previous experiences of respondents, the use of stated preference methods, the potential value of stated preference methods and the need for measures to facilitate using preferences. In this appendix the concepts are operationalized [62].

Questionnaire respondents' involvement

A first aspect assessed was how a respondent has been involved. Is this for instance in the PCWP, at a conference or via a WP? The exact question used stems from EMA's own survey on satisfaction [48]. A second question, also important for sub-group comparisons, is in what role this involvement was. The EMA makes a distinction between membership (e.g. of a scientific committee or the PCWP), representative of a patient organisation, expert and observer [44]. A third question was how patient organisations would categorize their involvement on the basis of the categorization by Rowe and Frewer (communication/consultation/participation) [8, 13].

The fourth and fifth question specifically assessed the extent to which respondents' involvement related to BRA. The fourth was whether or not patients' involvement allows them to provide input during BRA. The fifth question was an open question on the kind of input patients are using. Since the goal is to determine the added value of quantitative preferences there is a need to assess whether or not currently already preference-like data is being used.

The use of patient preferences

To assess the possible use of preferences it was assessed how preferences can be used based on when to use preferences, by whom they should be collected, in which cases they should be used, and what the motivation of patients is to personally use them.

When to use preferences

There are different moments when preferences can be used [63]. Based on an interview with Kim Wever [64] and input from patient organisations, patients might believe that preferences should be used before the final market authorization decision. Therefore, answer categories to this question included moments within the centralised procedure at the EMA, but also before (pre-clinical and clinical phases) and after (pharmacovigilance).

When to use preferences can also have implications for by whom the preferences should be used. Using them in the centralised procedure in principle implies that they will become part of CHMP discussions. It can however be that patient organisations want to personally use them whenever they think it is necessary, instead of standard including them in an assessment dossier. This does mean that once the preferences are used by patients they still become part of an assessment dossier.

Responsibility for the collection of preferences

The second aspect was who should collect the preferences. This is important since patients might not want the industry to collect preferences as they are worried that industry influences results [65, 66]. In addition, also after having the questionnaire discussed with patient organisations, an at least as important aspect was who pays for the preference elicitation [21, 64]. Possible answers for both questions are: the manufacturer requiring a market authorisation, the patients' and consumer's

organisations, the EMA, independent research institutes or universities, the healthcare professional's organisations and the NCA's from which the rapporteurs originate.

The cases in which to use preferences

The third aspect was in which cases preferences should be used. It is only when both the benefits and the risks of a drug are either high or low in principle interesting to use preferences [7]. Benefits and risks can also be seen as relative to another drug. In that case the use of preferences is only interesting when both the benefits and risks are higher compared to another drug, or both are lower compared to another drug. The following situations might be considered for using patient preferences: when the benefits are high, but there is also a relative high risk for multiple minor adverse effects; the benefits are high, but there is also a relative high risk for a fatal adverse effect; the benefits are low and there is a relative low risk for minor adverse effects; and the benefits are low and there is a relative low risk for a fatal adverse effect.

In addition to these options based on the benefit-risk balance there were some other options. The first is when there is no drug yet for a particular disease and there is a high necessity or pressure/demand from society to come up with a drug [7]. This option was split into three options, as suggested by a patient organisation. There are cases in which there are no medicines at all, cases when the current medicines are not sufficient and rare disease cases. Another option is when evidence is only based on a particular group, but when approval is sought for a wider audience [7]. A final option is when there is relative much uncertainty surrounding the data on benefits and risks.

Motivation to use preferences

The fourth aspect concerned the role of patients regarding the use of patient preferences. It can be that patients are personally confronted with preferences, for instance when consulted in a benefit-risk discussion in which preferences are also available as evidence. The question was how patients think about a personal active role in these discussions of the preferences (i.e. combining direct involvement and preferences). For this possible use by patients it is important to recognize some institutional barriers identified by Petts [24] for participation, including regulatory fragmentation, lack of regulatory support, institutional paternalism [22] and an expert culture. These might decrease the motivation of patients to personally get involved. Instead of asking whether or not patients personally want to use preferences, it was therefore assessed what the motivation of patients is to use preferences [67].

Motivation refers to whether or not a person is moved to do something, in this case to use preferences [68]. Most interesting is the extrinsic motivation; motivation based on achieving a particular outcome [69]. To measure this, the valence-instrumentality-expectancy theory, a descriptive decision theory presented in figure 2, was used [67].

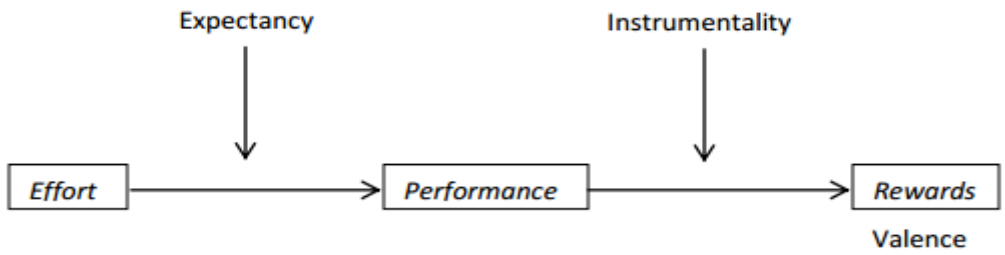


Figure 2: basic expectancy model [67]

Expectancy is the subjective probability that an effort will lead to a level of performance. This expectancy ranges from 0 to 1 where 0 is no chance that the effort will lead to a certain level of performance, and 1 is certainty that an effort will lead to a level of performance. Instrumentality is about whether a performance that is achieved also leads to certain rewards, or work outcomes. This is also a subjective probability resulting in a score between 0 and 1. Valence refers to the value or preferences for a particular reward. Valence can be either positive or negative, resulting in a score between -1 and 1. Zero indicates indifference [67]. To measure the motivation the following definitions were given to effort, performance and rewards.

Table 4: meanings of effort, performance and rewards

Item	Definition
Effort	Personal ability to properly apply preferences in EMA activities on benefit-risk decisions
Performance	Proper use/representation of preferences in EMA activities on benefit-risk decisions
Rewards	Impact of patients views on benefit-risk decisions

The expectancy of effort leading to performance is the expectancy that the use of patient preferences by a patient will lead to a proper use of preferences; do representatives thus think they are able to handle the preferences in their involvement? Instrumentality as the probability of performance leading to rewards is the probability that the use of preferences will lead to an impact of patients' views. To keep the length of the questionnaire within limits only one level of performance is used [70]. Valence is seen as the importance that is attached to achieving impact of patient's views.

Scores on the three items were gathered by stating questions quite similar to questions used by Dillard [88]. For expectancy and instrumentality the perceived likelihood was assessed with the following possible responses: no chance, little chance, fairly good chance, good chance, extremely good chance. For valence, instead of Dillards desirability, importance was used, which is according to literature possible [71]. Validity regarding the items is sufficiently present in Dillards conceptualization, although in this study adjusted statements were used, and only one item per construct was used instead of multiple. The final step is to multiply the scores on the three aspects. This results in a motivational force. Multiplying indicates that one score of zero results in an overall motivation of zero, even if the other two scores are high [67].

The possible value of patient preferences

In order to judge the added value of using patient preferences several criteria have been used. The difference on these criteria between the current situation and the hypothetical use of preferences was considered the added value of patient preferences. To obtain the criteria, two approaches were used.

The first was a framework for evaluating participation exercises by Rowe and Frewer [37] consisting of acceptance and process criteria. Four acceptance criteria were used: influence, early involvement, transparency and representativeness. Considering transparency, preferences might contribute to (clarifying) how patients are involved, but also to (clarifying) how decisions are reached. Early involvement was used as it is important to involve patients as soon as value judgements become important [37]. Theoretically one could also argue that preference data increase the awareness of the public on possible differences between drug characteristics and preferences, and thus of when they should become involved or active. Representativeness was used to assess the representativeness of current involvement and the extent to which preferences can increase this. More data on patients' opinions might increase the representativeness of the patients or patient views involved [17]. With influence was meant that patient views should have an impact on the decisions made. It is interesting to consider the extent to which patients' views are considered since the preferences are explicitly about benefits, risks and the trade-offs between the two. Since patients can according to the EMA enrich decisions and provide valuable insights [26-28], assessing the influence was also logical. Another reason to use these criteria from Rowe and Frewer was that they have already developed questionnaires to assess the items [41]. The following definitions belong to the criteria.

Table 5: acceptance criteria by Rowe and Frewer [37]

Criteria	Definition
Representativeness of participants	A representative sample of the public representing public interest, rather than a subset of (own) interests
Early involvement of participants	The public should be involved as early as possible (as soon as value judgment becomes salient)
Influence	The output of the procedure should have a genuine impact on the benefit-risk decisions made
Transparency	The process of involvement and decision making should be transparent

The criteria are in principle meant for evaluating direct single participation exercises. However, in this study they were used to assess the value of patient preferences. Rowe and Frewer have developed a longer and shorter questionnaire, consisting of multiple or just one item per attribute. The questions used in this research are from both questionnaires, depending on the criterion. They were slightly adjusted to reflect that it is about patient involvement and preferences in BRA, and to reflect the entire spectrum of involvement possibilities relating to BRA. The questions to address the four attributes, were given as statements that can easily be answered on an agree – disagree scale. The reliability and validity of the questionnaires has proven to be good [41]. Before the four attributes were addressed, an open question was used to assess what the respondents think is important for successful involvement in benefit-risk assessment. This was done to validate the use of the four theory-based criteria. In the questionnaire this question was placed before the criteria were assessed to prevent that they bias the responses [41].

The second approach that was used concerned a decisional conflict scale which assesses the level of decisional conflict; a state of uncertainty, normally experienced by a patient in choosing a treatment [38, 39]. This scale can be used to assess how decision aids contribute to decreasing the uncertainty. Normally, aids are used at the individual patient level, but in this case the scale was translated to assess the value of preferences, the aid, for involvement in BRA. Also, the scale was used at a higher

level; the EMA level instead of the patient level. Using the decisional conflict scale is considered relevant as drug assessments are characterized by uncertainty, both about the decision as the data. The relevance of using the decisional conflict scale did however also depend upon the extent to which patients are directly (motivated to be) involved in BRA. When the patient preferences are only discussed by the EMA experts, the scores on the scale have less relevance as patients will be less informed by the preferences.

The decisional conflict scale consists of the dimensions uncertainty in making a choice, factors contributing to uncertainty and perceived effectiveness of the decision [38]. The factors contributing to uncertainty are 1) being uninformed about alternatives, benefits and risks; 2) being unclear about personal values; 3) experiencing pressure and no support from others and 4) having skills deficits [39]. Because the initial decisional conflict scale consists of 16 items the choice was made to use the SURE scale (SURE – Sure of myself; Understand information; Risk-benefit ratio; Encouragement) which consists of only 4 items. This scale, presented in table 6, meant for identifying decisional conflict among patients in clinical situations, was translated to the use of preferences in patient involvement in BRA. The scale only focuses on the first (uncertainty in the decision) and the second dimension, which consisted of the three factors contributing to uncertainty. The perceived effectiveness of the decision is not part of the SURE scale, but neither would that dimension have been applicable to this case [40]. The items were measured on a five-point Likert scale from strongly disagree to strongly agree [40, 72]. For the SURE scale, validity and reliability have been proven to some extent [73].

Table 6: sure scale [40]

SURE acronym - item	Original question
Sure of myself	Do you feel sure about the best choice for you?
Understand information	Do you know the benefits and risks of each option?
Risk-benefit ratio	Are you clear about which benefits and risks matter most to you?
Encouragement	Do you have enough support and advice to make a choice?

Measures to facilitate the use of patient preferences

Current benefit-risk assessment and patient involvement at the EMA might not be optimally suited for the use of patient preferences. When no added value in using preferences is found, the need for possible measures is important for making a distinction between the preferences and the process as reasons why preferences are not considered useful, and thus for determining the potential of preferences. Unsuitability of the current process might be due to institutional [74] or contextual factors, for instance a lack of regulatory support [42]. Therefore, patients might suggest a need for particular measures in BRA to be taken.

Gagnon et al [12] have identified barriers and facilitators of patient involvement from different studies. These can also be related to patient involvement with quantitative patient preferences. Other useful suggestions were made in articles from Bowman-Busato and Oliver et al [21, 75]. Additionally some (similar) factors were identified from the European Patients Forum studies on patient involvement in health technology assessment (HTA) [76-78]. Finally, suggestions were taken from the interviews and contacts with patient organisations [64].

Appendix 2: Questionnaire

THE POSSIBLE USE OF QUANTITATIVE PATIENT PREFERENCES AT THE EMA

Dear respondent,

Thank you for participating in our research. In EMA's benefit-risk assessments the benefit-risk balance of a medicine should be favourable. Within the EMA patients are involved. This questionnaire explores **the use quantitative patient preferences as a possibility for more regular involvement in benefit-risk assessments**. Quantitative patient preferences refer to patients' values for medicines or particular benefits and/or risks of these medicines.

The questionnaire consists of three parts. First, some questions are posed on **your involvement**. Secondly, questions are asked about **how you think quantitative preferences could be used** in EMA's benefit-risk assessments. Third you are asked about **how these preferences could support patient engagement in benefit-risk assessments.**

This questionnaire should in total only take 20 minutes of your time. Most questions can be answered by checking one or multiple boxes. Sometimes you are asked to clarify your answers. It is **possible to save your answers and resume at a later time**.

There are 17 questions in this survey.

A note on privacy
This survey is anonymous.
The record kept of your survey responses does not contain any identifying information about you unless a specific question in the survey has asked for this. If you have responded to a survey that used an identifying token to allow you to access the survey, you can rest assured that the identifying token is not kept with your responses. It is managed in a separate database, and will only be updated to indicate that you have (or haven't) completed this survey. There is no way of matching identification tokens with survey responses in this survey.

0% 100%

Part 1 - Your involvement in EMA's benefit-risk assessments

Benefit-risk assessments at the EMA

The assessment for the **market approval** of medicines for human use **can be done by different scientific committees**. An important one with general responsibility for the assessments is the Committee for Medicinal Products for Human Use (CHMP). **In addition to the CHMP there are other scientific committees for benefit-risk assessments like the Committee for Advanced Therapies (CAT) and the Pharmacovigilance Risk Assessment Committee (PRAC).** The main route of authorisation is the **centralised procedure**. At the end of the procedure the scientific committee gives an **opinion on the market authorization**. This opinion is most often followed by the European Commission. (Note: this questionnaire is about benefit-risk assessments and patient involvement in those at the EMA, it is not about the mutual recognition and decentralised procedures).

1
In which of the following EMA activities have you been involved?

- ☐ Member of the Management Board
- ☐ Member of a scientific committee (please specify to COMP, PDCO, PRAC or CAT)
- ☐ Member of the Patients' and Consumers' Working Party (PCWP)
- ☐ Member of a certain network (please specify to ENCePP, Enpr-EMa, or another)
- ☐ Guideline preparation (please specify via which working party)
- ☐ Product related issues (e.g. SAGs/WPs/scientific committee consultations, participation in meetings) (please specify the activity and the committee, SAG or WP)
- ☐ Participation in/consultation by specific working groups (please specify the specific working group)
- ☐ Review of information (e.g. EPAR summaries, package leaflets, safety communications (including training))
- ☐ Participation in stakeholder meetings relating to the new pharmacovigilance legislation
- ☐ Conferences/workshops/info sessions organised by the EMA (please specify the activity)
- ☐ None
- Other: ☐

? Please specify your answer if requested in the option.

2
In what role did you participate?

- ☐ Member (e.g. of the PCPW or a scientific committee)
- ☐ Representative of a patients' and consumers' organisation
- ☐ Expert (please specify if this also was as a patient with the disease relevant to the involvement)
- ☐ Observer
- ☐ Do not know
- Other: ☐

? If multiply apply, please specify the activities, indicated at question 1, for each role.

3
It is possible to distinguish three categories of involvement:

- **Communication: a one-way transfer of information from the EMA to patients. I was informed by the EMA on relevant issues.**
- **Consultation: a one-way transfer of information from patients to the EMA, after a request from the EMA. I was consulted by the EMA on relevant issues.**
- **Participation: a two-way transfer of information between the EMA and patients. I.e. a dialogue in which opinions can be shaped.**

What would best describe your overall way of involvement as specified at question 1?

- ○ Communication
- ○ Consultation
- ○ Participation
- ○ Other: ☐

4
Did or does your involvement, as specified in question 1, allow you to provide input or comment on (particular aspects of) benefit-risk assessments (for market authorization) of the EMA?

- ◉ Yes, on the entire benefit-risk balance
- ○ Yes, but only on aspects of the benefit-risk balance
- ○ No
- ○ Do not know

Please enter your comment here: ☐

? If you have been involved in multiple activities (question 1), please use the box on the right to specify for which activity you have provided input/commented on (particular aspects of) benefit-risk assessments.

5
What kind of information do you or does your organization use to provide input on benefit-risk assessments at the EMA? Aspects you could mention are the kind of information, the source of information, the aspects of a drug the information relates to, to whom this input is expressed and the way this input is expressed.

☐

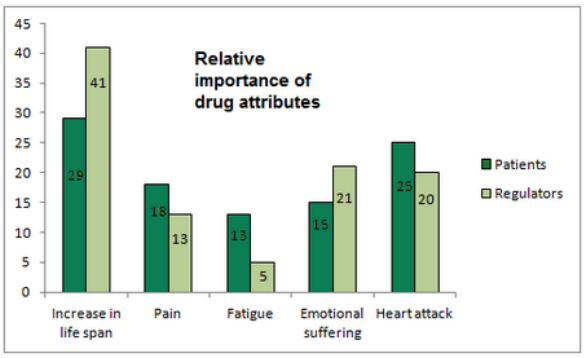
0% 100%

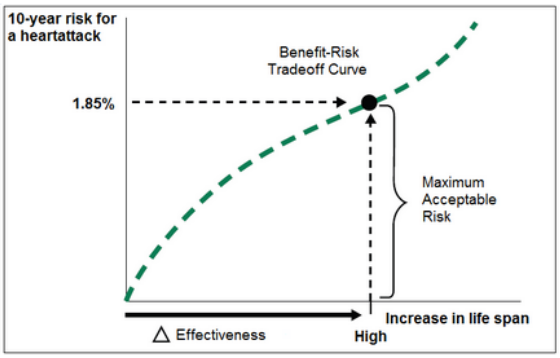
Part 2 - Using preferences in the benefit-risk assessments

In this second part questions are asked about how the quantitative patient preferences might be used in benefit-risk assessments at the EMA.

Explanation

With quantitative patient preferences, aspects of treatments are numerically valued by patients. The focus of the preferences can be on the benefits, risks, trade-offs between these two, the entire treatment, and also on aspects like treatment frequency or administration mode. The numerical representation of patient preferences can make possible differences in views between patients and regulators more explicit. Consider the following two examples which relate to a hypothetical medicine. In the left figure you can see the relative importance of different attributes of the hypothetical treatment, and the differences in this between the patients and the regulators. In the right figure you can see the trade-offs patients are willing to make between a certain increase in life span, and a 10 year-risk on a heart attack. The maximum risk patients would tolerate for a high increase in life-span is 1.85% per 10 year.





(Figures based on: Muhlbacher, A.C. and M. Nubling, Analysis of physicians' perspectives versus patients' preferences: direct assessment and discrete choice experiments in the therapy of multiple myeloma. European Journal of Health Economics, 2011. **2011**(12): p. 193-203.
Johnson, F.R. and A.B. Hauber, Quantifying Patient Benefit-Risk Tradeoff Preferences: A Brief Introduction - White paper, 2008.)

6

If quantitative measures of patient preferences would be used in the benefit-risk assessment of a drug, when do you think they should be used as input in the procedure? (Note: the first two options are during the development of a medicine. The other options are related to the market authorisation).

- ☐ Before submitting an application for authorisation: in pre-clinical research
- ☐ Before submitting an application for authorisation: in the ethics committees/clinical trials
- ☐ In the initial marketing authorisation application (submitted by the sponsor)
- ☐ During the authorisation procedure (after the initial application, but before a decision is reached)
- ☐ After the market authorisation (for example when pharmacovigilance activities show a higher risk profile than expected during the authorisation)
- ☐ During the authorisation procedure, but not necessarily in an application as part of scientific committee discussions, they should only be used by patient organizations at the moment considered appropriate (e.g. in consultation by the scientific committees, SAG's or WP's)
- ☐ During the authorisation procedure, but not always in an application as part of scientific committee discussions, they should only be used by the scientific committees at the moment considered appropriate
- ☐ Do not know
- ☐ Other: [ ]

7

When quantitative measures of patient preferences are used in the benefit-risk assessment of a drug, two important aspects regarding the collection of these data are the reliability of the data and the costs of collecting the data.

Who would you trust most in collecting reliable data?

- ○ The pharmaceutical manufacturer/applicant
- ○ The patients' and consumers' organizations
- ○ The EMA
- ○ The national competent authorities where the rapporteurs originate from
- ○ Independent research institutes or universities
- ○ Healthcare professionals' organizations
- ○ Do not know
- ○ Other:

[ ]

8
Who should cover the costs of collecting the patient preference data?

- ○ The pharmaceutical manufacturer/applicant
- ○ The patients' and consumers' organizations
- ○ The EMA
- ○ The national competent authorities where the rapporteurs originate from
- ○ Independent research institutes or universities
- ○ Healthcare professionals' organizations
- ○ Do not know
- ○ Other:

9
In which cases do you feel it is important to consider quantitative patient preferences in benefit-risk assessments?

- ☐ High benefits, relative high risk for multiple minor adverse effects
- ☐ High benefits, relative high risk for a fatal adverse effect
- ☐ Low benefits, relative low risk for minor adverse effects
- ☐ Low benefits, relative low risk for a fatal adverse effect
- ☐ In the case of a new medicine in a area of unmet medical need (current medicines are not sufficient)
- ☐ In the case of a new medicine in a area of unmet medical need (there is no current medicine)
- ☐ In the case of a new medicine for rare diseases
- ☐ When evidence is mainly about benefits and risks for a particular group (e.g. age 30 to 50), but when approval is sought for a wider or other audience than that particular group
- ☐ In the case that there is relative much uncertainty surrounding the data on benefits and risks of a medicine
- ☐ Always
- ☐ Never
- ☐ Do not know
- ☐ Other:

10
This question and the following two (11 and 12) are about the possibility of your (organizations') personal use of preferences. This can for example be the case when you are asked to participate in discussions which might include preferences, or when you have preferences available to you or your organization and which can be used to express your opinion in consultations by for example the scientific committees and their SAG's.

	What is the chance that you personally will be able to properly apply quantitative patient preferences?
No chance	○
Little chance	○
Fairly good chance	○
Good chance	○
Extremely good chance	○

11

	What is the chance that a proper use of quantitative patient preferences contributes to the patient views having impact on the benefit-risk decisions of the EMA?
No chance	○
Little chance	○
Fairly good chance	○
Good chance	○
Extremely good chance	○

12

	How important for you is the consideration/impact of patient views in benefit-risk decisions of the EMA?
Very unimportant	○
Unimportant	○
Neutral	○
Important	○
Very important	○

0% 100%

Part 3 - Added value of patient preferences (1)

In this third part questions are asked about the relation between patient involvement, both with and without the use of preferences, and benefit-risk decisions. The main question is: what can preferences add to representing patients' views, when used as you indicated in the previous questions? When we talk about patient representatives in the following questions, we also mean patient experts, observers and members of committees.

13

What do you feel are important criteria for successful involvement (of patients and their organizations) in EMA's benefit-risk activities?

0% 100%

Part 3 - Added value of patient preferences (2)

14

Please indicate the extent to which you agree or disagree with the following statements, assuming patient representatives do not have any knowledge/availability of quantitative patient preferences (the current situation).

	Strongly Disagree	Disagree	Neither disagree nor agree	Agree	Strongly Agree
The patient views expressed in EMA activities relating to benefit-risk assessments are representative of those who are affected by the benefit-risk decisions	○	○	○	○	○
Involvement in benefit-risk assessments is taking place too late to allow patients representatives to influence benefit-risk decisions	○	○	○	○	○
Patients' views regarding benefit-risk issues are taken seriously in benefit-risk assessments	○	○	○	○	○
Patients' views regarding benefit-risk issues are influential on the benefit-risk decisions made by the EMA	○	○	○	○	○
It is clear how the results of patient representatives' involvement in benefit-risk assessments are used	○	○	○	○	○
Patient representatives are sure about the position to take in benefit-risk assessments	○	○	○	○	○
Patient representatives are aware of the benefits and risks of a drug when involved in benefit-risk assessments	○	○	○	○	○
Patient representatives are aware of which benefits and risks are most important to the patient population when involved in benefit-risk assessments	○	○	○	○	○
Patient representatives have enough support and information in their benefit-risk involvement to take a position in benefit-risk assessments	○	○	○	○	○

0% 100%

Part 3 - Added value of patient preferences (3)

15
Please indicate the extent to which you agree or disagree with the following statements, assuming patient representatives now do have knowledge/availability of quantitative patient preferences (in addition to the current involvement processes).

(this can for example mean that patients are involved in benefit-risk discussions which include preferences, but it can also mean the use of preferences in EMA discussions without the direct involvement of patient representatives, in which case the preferences are the representation of views or way of involvement)

	Strongly Disagree	Disagree	Neither disagree nor agree	Agree	Strongly Agree
The patient views expressed in EMA activities relating to benefit-risk assessments are representative of those who are affected by the benefit-risk decisions	○	○	○	○	○
Involvement in benefit-risk assessments is taking place too late to allow patients representatives to influence benefit-risk decisions	○	○	○	○	○
Patients' views regarding benefit-risk issues are taken seriously in benefit-risk assessments	○	○	○	○	○
Patients' views regarding benefit-risk issues are influential on the benefit-risk decisions made by the EMA	○	○	○	○	○
It is clear how the results of patient representatives' involvement in benefit-risk assessments are used	○	○	○	○	○
Patient representatives are sure about the position to take in benefit-risk assessments	○	○	○	○	○
Patient representatives are aware of the benefits and risks of a drug when involved in benefit-risk assessments	○	○	○	○	○
Patient representatives are aware of which benefits and risks are most important to the patient population when involved in benefit-risk assessments	○	○	○	○	○
Patient representatives have enough support and information in their benefit-risk involvement to take a position in benefit-risk assessments	○	○	○	○	○

0% 100%

Part 3 - Added value of patient preferences (4)

16
To contribute to the use of quantitative patient preferences at the EMA, what do you think should change?

- ☐ Nothing, I do not think quantitative patient preferences could contribute at all in the current benefit-risk assessment processes at the EMA
- ☐ Nothing, I think the current processes at the EMA offer sufficient possibilities for the use of quantitative patient preferences
- ☐ Increase the level of involvement of patient representatives regarding benefit-risk assessments of drugs
- ☐ Assign one or multiple patient representatives to the CHMP
- ☐ Assign a certain weight to the importance of the patient preferences in assessments
- ☐ Provision of education and support regarding (the use of) quantitative patient preferences to patient representatives
- ☐ Provision of education to EMA's scientific committees' decision makers about patients' preferences and real-life experiences
- ☐ Provision of information on the influence of patient views on decision-making to patient representatives
- ☐ Provision of easy summaries of assessment reports (incl. preferences) to patient representatives
- ☐ A decrease in the technical difficulties (complexity of information in assessment reports) of the assessments for patient representatives
- ☐ Easy access to key reports/protocols in an assessment for patient representatives
- ☐ Assign (more) EMA personnel to support patient involvement
- ☐ Provide more money to patient representatives so they can actively pursue involvement in benefit-risk decisions
- ☐ Other: [ ]

17
You have answered all questions. If you have any comments relating to a question, the questionnaire, or in general, please use the textbox below.

[ ]

Appendix 3: Qualitative document analysis

The goal of the document analysis was to analyse the current patient involvement in BRA on the basis of documentation. It is known that policy documents do include information on patient involvement in benefit-risk assessment. An important follow-up question is if patients are also really involved in BRA and possibly what is being done with their views, for which documentation could be a good indicator [62]. The question is therefore what documents besides policy documents include about patient involvement in BRA. If for instance assessment reports do not include patient involvement in benefit-risk assessment, it is interesting to notice what this means in relation to the established policy. Although there are reasons for using a quantitative content analysis over a qualitative document analysis, e.g. for being able to use statistical tests for validity, a choice for a document analysis has been made to grasp the unique and complex situation at the EMA [79]. Also, the ambiguities in the documents have forced this study into a qualitative direction.

Sample

There are three categories of documents in which information about patient involvement and BRA was expected. First there were policy documents stating how the EMA involves patients. Secondly there were so-called progress documents like the yearly reports on interaction. These discuss the policy execution. Thirdly, there were drug assessment reports, which were used to evaluate the extent to which patients have really been involved in assessments, and on which aspects.

The analysed documents are both the units of observation as the units of analysis. Several types of documents were selected of which it was expected that they could involve information on patient involvement and patient views, or which simply are about patient involvement. This can also be called purposive or judgmental sampling [62]. In the paper the precise way of collection has been described. Overall 45 documents retrieved from the EMA were selected via EMA's website in the period May-June 2013.

Table 7: documents used for content analysis

Source/kind of document	#	Document	Category of document	Sampling technique if there are multiple documents
Drug authorizations	A1	EPAR summary Temozolomide Sun (2011)	Assessment	Random selection of 2 per year over 2011-2013
	A2	EPAR summary Selincro (2013)		
	A3	EPAR summary Jetrea (2013)		
	A4	EPAR summary Constella (2012)		
	A5	EPAR summary Zoledronic Acid Hospira (2012)		
	A6	EPAR summary Matever (2011)		
	A7	Public assessment report Buccolam (2011)		Random selection of 2 per year over 2011-2013
	A8	Public assessment report Docetaxel Accord (2012)		
	A9	Public assessment report Zoledronic acid medac (2012)		
	A10	Public assessment report Tolucombi (2013)		
	A11	Public assessment report Voriconazole Accord (2013)		
	A12	Public assessment report Bydureon (2011)		
	P13	Road map to 2015 - The European Medicines Agency's contribution to science, medicines and health	Policy	
	P14	EMA flyer 'Working with patients and consumers'		
	P15	Framework on the interaction between the European Medicines Agency and patients' and consumers' organisations		

General documents on patient involvement	P16	Rules of involvement of members of patients'/consumers' and healthcare professionals' organisations in committees related activities		
	P17	The role of patients as members of the EMA Human Scientific Committees		
	PR18	Implementing the European Medicines Agency's Road Map to 2015: The Agency's contribution to Science, Medicines, Health	Progress/policy	
	PR19	Reflection paper on the further involvement of patients and consumers on the agency's activities		
	PR20	(First) Report on the progress of the interaction with patients' and consumers' organisations	Progress	
	PR21	Second report on the progress of the interaction with patients' and consumers' organisations		
	PR22	Third report on the progress of the interaction with patients' and consumers' organisations		
	PR23	Fourth report on the progress of the interaction with patients' and consumers' organisations		
	PR24	Fifth report on the progress of the interaction with patients' and consumers' organisations		
CHMP	P25	Final CHMP-work programme 2011-2013	Policy	
	P26	Mandate, objectives and rules of procedure for the scientific advisory groups (SAGs) and ad-hoc experts groups		
	P27	CHMP Workplan 2008-2010 ''Specialised Experts and SAGs: Optimisation of Consultation process from CHMP		
	PR28	Outcome report on pilot phase for participation of patient representatives in Scientific Advisory Group meetings	Progress	
	A29	CHMP meeting highlights 27-30 May 2013	Assessment	Random sample of 2 per year from the highlights from 2011-2013
	A30	CHMP meeting highlights 18-21 February 2013		
	A31	CHMP meeting highlights 12-15 November 2012		
	A32	CHMP meeting highlights 16-19 April 2012		
	A33	CHMP meeting highlights 14-17 November 2011		
	A34	CHMP meeting highlights 17-20 October 2011		
PRAC	P35	Countdown to July 2012: the establishment and functioning of the PRAC	Policy	
	A36	Minutes of the PRAC meeting 8-11 April 2013	Assessment	Random sample of 2 per year from the minutes for the years 2012-2013
	A37	Minutes of the PRAC meeting 7-10 January 2013		
	A38	Minutes of the PRAC meeting 29-31 October 2012		
	A39	Minutes of the PRAC meeting 1-3 October 2012		
PCWP	P40	Mandate, objectives and rules of procedure for the European Medicines Agency Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP) (2010 and 2013 version)	Policy	
	P41	Work plan for the European Medicines Agency Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP) 2013		
	PR42	Minutes of EMA Human Scientific Committees' Working Party with (PCWP) meeting with all eligible organisations Patients' and Consumers' Organisations 30 November 2012	Progress	Random sample of 1 per year from the minutes for the years 2011-2013
	PR43	Patients/Consumers Working Party (PCWP) and Healthcare Professionals Working Group (HCPWG) joint meeting 27-28 February 2013		
	PR44	Minutes of the EMA Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP) with all eligible organisations - meeting of 30 November 2011		
MB	P45	Rules of procedure of the Management Board	Policy	

Besides general policy documents on patient involvement, documents were taken from the PRAC, CHMP and PCWP. Progress reports were taken from the PCWP, CHMP and yearly reports on interaction with patients and consumers. PCWP minutes are considered progress reports since the PCWP is specifically for patient involvement. For the group of assessment documents EPAR summaries and the more extensive assessment reports have been selected since they report on the

benefit-risk assessments. In addition, benefit-risk issues are also discussed in the CHMP and the PRAC of which minutes/highlights of meetings are taken. PRAC minutes are also considered 'assessments' since the goal of this committee relates to pharmacovigilance. It would have been interesting to also include minutes of SAG meetings, but unfortunately these minutes are not publicly available. Because of reasons of time and an increase in attention for involvement in BRA, no documents older than from 2011 are used, except for certain policy and progress documents.

Analysis

In analysing the documents it is possible to take parts of documents and entire documents as the units of observation [62, 80]. The latter was done because a preliminary scan of the documents showed a high likelihood of finding little information on patient involvement in BRA in certain documents. In the results table the findings on patient involvement (in BRA) are presented.

Patient involvement at the EMA

First, a general overview of how patient involvement at the EMA is operationalized is provided. This helps placing the findings from the document analysis on patient involvement in BRA in the proper context.

EMA's policy on patient and consumer involvement

Current patient involvement at the EMA is mainly based on the Framework on the interaction between the EMEA and Patients' and Consumers' Organisations. The EMA tries to contribute to the empowered patient by providing information adapted to the patients needs, develop appropriate communication tools, and increase the awareness of patients in relation to the use of medicines [25]. The achievement of these three objectives consists of two main parts (discussed below) in which cooperation should be developed. The first part is the implementation of the involvement parts of new legislation (EC No 726/2004 and Directive 2004/27/EC). The second part is about a platform of exchange between the EMA and patients; the PCWP. Currently most goals in the framework are met [81]. A revision of the framework should become available by the end of this year (2013).

The organisations

The EMA has defined patient organisations as ''not-for-profit organisations which are patient focused, and whereby patient and/or carers represent a majority of members in governing bodies''. These can be general umbrella organisations, ''representing European specific disease organisations and/or national umbrella organisations'', or European disease specific organisations, ''representing national organisations or individual patients''[82]. Based on eligibility criteria there are currently 34 organisations involved in EMA activities.

The organisations, their representatives or patients can participate in multiple ways at the EMA. A first is membership of a body on behalf of a patient organisation. A second option is to participate in meetings of different committees as a representative of an organisation. A third option is an expert in a particular area. These experts act on their own behalf and do thus not necessarily represent their organisations view [49]. The fourth option is to participate as an observer. This looks quite similar to being a member, albeit without the right to participate in the conclusions and decisions [44].

Implementation of the new legislation

Based on Regulation (EC) No. 726/2004 two of the 35 members of the EMA's management board are representatives of patient organisations [27, 83]. The main role of this board relates to budgetary and planning affairs, and monitoring the overall performance [84]. In addition to being a member it is also possible for patient organisations to be informed and/or consulted by the management board and to participate in agency's activities as observers [25].

A second way of patient involvement is through the scientific committees. Involvement is taking place by means of membership of the COMP, CAT, PRAC and PDCO [27]. The CHMP does not have any patient members, although based on regulation No. 726/2004 they shall on an advisory basis have contact with representatives of patient organisations. Important is the distinction between expert and representative were experts have to sign a confidentiality agreement [49].

Where involvement via the scientific committees and management board has a specific legal basis; all of the following ways are based on Regulation (EC) No. 726/2004. The CHMP can interact with patients through their SAG's, WP's and rapporteurs. SAG's shall establish contacts on an advisory on ''very specific issues related to disease management or its impact on the day-to-day life of the patients'' [25]. According to the EMA interactions in these SAGs can also provide valuable insight in for instance acceptable levels of associated risks [53]. Where SAG's are mainly meant for answering scientific questions on a consultative basis, WP's can be delegated tasks associated with scientific guidelines [46]. WP's are like the SAG's not allowed to address the entire benefit-risk balance [85]. Issues to be discussed with patients by the WPs are issues like the quality of life or feasibility of clinical trials. A final possibility for consultation by the CHMP is through the rapporteurs. These can consult patients when ''relevant to the indications of the medicinal products concerned'' [25]. This means representation by patients' organisations.

The PhVWP has one permanent patient representative as observer. In 2012 it transformed into the PRAC. The mandate of the PRAC relates to the risk management of products. Currently, the PRAC includes a representative of a patient organisation as a full member [44, 86]. Tasks of the patients in the PRAC include assessing what risks are acceptable, or what balance of benefits and risks is favourable [87].

Besides the interaction with the scientific committees the framework also includes some provisions related to public information. The quality of the information provided to patients should be increased by making EPAR's understandable to the public, increase the readability of package leaflets and ''consult with target patient groups to ensure that the package leaflet is legible, clear and easy to use'' [25]. Secondly, additional information should be provided about the agency's activities. In addition to reviewing information patients and consumers are usually involved in a number of additional initiatives like clinical trials in third countries, workshops, conferences, meetings and other ways of involvement [26, 48].

Patients' and Consumers' Working Party

The second part of the framework on interaction related to the establishment of the Patients' and Consumers' Working Party. This working party, in which currently 15 PCO's have a seat, is especially for interaction with patient organisations. The mandate of the PCWP is to ''provide recommendations to the EMA and its Human Scientific Committees on all matters of direct or

indirect interest to patients in relation to medicinal products'' [88]. One of the tasks is to provide advice on product specific matters, albeit upon request of one of the EMAs scientific committees [88]. Product related issues include reviews of the package leaflet and safety communications, provide input for new Pharmacovigilance legislation and other pharmacovigilance issues, and contributing to transparency on medication.

Results

Policy documents

First, the policy documents include patients and their involvement in BRA to a different degree. Of the general policy documents, the roadmap to 2015 and its plan of implementation include it, but only some information as these documents are about all kinds of EMA activities. Considering these documents, patients' contribution in BRA is considered important as they enrich regulatory decisions. But also for other issues, for instance involvement on guidelines development and benefit-risk communication their involvement is considered valuable. Overall, according to the roadmap to 2015, the EMA wants to contribute to the empowered patient concept.

Considering the involvement of patients specifically in BRA according to the policy documents, this is low. The task of the management board does not include BRA. They only have a supervisory role. Of some scientific committees patients are by membership involved in judgements, but a problem here is the absence of CHMP membership, and the confidentiality agreement for experts. Patients can also be involved in BRA within the CHMP by consultations [25]. This involvement however seems to be on an ad-hoc basis [44], and not always directly related to benefit-risk aspects or the benefit-risk balance. A more structured way of patient involvement takes place through the SAG's who can provide recommendations on scientific/technical matters for products under evaluation [45], for instance by the continued pilot of structural patient involvement. The limitation here is that SAG's do not reflect on the entire balance, do not directly assess benefit-risk, and questions are asked on initiative by the CHMP. Also, confidentiality applies to the SAG meetings. Patients are involved in BRA via the PRAC. The limitation here is that it only concerns pharmacovigilance activities and also here not the entire balance is assessed. Another important patient forum is the PCWP. Although they have a broad mandate, it does not seem this is directly related to BRA, and when providing advice this is only upon request of the EMA [88, 89]. Also, the PCO's can only present their views. They cannot participate in the scientific deliberations of the CHMP through the PCWP [54] (this latter is based upon literature).

A final important finding from the policy documents is that (ranging from 2009 to 2013) it is stated that a new definition on involvement of patients in BRA, ultimately also leading to patients utilities being taken into account, should become available as part of the revised framework on interaction. Overall the policy documents show that patient representatives and their organisations are involved in BRA, but this involvement also seems low and obstructed by multiple barriers for patient involvement.

Progress documents

An important conclusion from the reflection paper (2009) is that further involvement in BRA of patients should be explored given the diverse advantages attached. The yearly reports on interaction show from the first year on that the framework on interaction has been fully implemented. Further, they show that overall involvement of patients has grown.

Looking at possible involvement specifically in BRA, this seems low as part of overall involvement. When involved in BRA this is mainly done via the scientific committees and the SAG's. CHMP consultation has taken place a couple of times on an ad-hoc basis for products under evaluation on issues like safety information, current use of a product and availability of a medicine. Considering some examples, it is seen that via the committee's patients have been consulted on risk management plans for lenalidomide and thalidomide, and regarding Onsenal and Prezista patients have been asked questions on the use of these drugs. An example of consultation via a working party is participation of patient experts in the scientific advice working party. This has happened thirteen times in both 2010 and 2011 relating to issues on protocol assistance [26, 48], thus not addressing the benefit-risk balance. Via SAG's patients have on an increasing base been consulted in BRA. The past years ten to twenty times a year [26, 48]. They have for example been consulted on the impact on the day-to-day life of Tysabri and many other drugs. Most often however the aspect of a drug upon which patients are consulted is not known, which makes it difficult to determine whether their contribution relates to BRA or not. At the times the subject of contribution is clear, this does not directly relate to judging benefits and risks. The pilot phase of patient involvement in SAG's shows mixed opinions among the SAG chairs and rapporteurs on the value of patient involvement. The evaluation of the pilot also shows that while there is some minor involvement in BRA, the limitations previously mentioned are also confirmed. Questions are posed in advance which means patient representatives cannot freely comment on the benefit-risk balance, exact contributions are not known because of the confidentiality agreements, the patient representatives seem limited in their knowledge and there is no commenting on the entire benefit-risk balance. A final important way of interaction is via the PCWP. In 2010, 2011 and 2012 there have been four meetings a year. Based upon minutes of meetings the PCWP is involved in the development of a definition on how patients are and should be involved in benefit-risk assessments. Further, while the policy documents already implied it, the minutes of PCWP meetings clearly show that via the PCWP patients are not involved in the judgement of benefits and risks.

Besides the diverse ways in which patients have been involved, it is interesting to notice that the framework on interaction should have been revised in 2010/2011 (third report on interaction), which has changed to 2011/2012 (fourth report on interaction), and which has currently (December 2013) still not happened.

Overall the progress documents do show some involvement in BRA, but not much. Also when specific cases are mentioned, the EMA seems to take a 'broad' definition of benefit-risk when talking about patient involvement. For instance, the EMA sees SAG involvement of patients as involvement in benefit-risk assessment, however when involved the issues discussed are posed as questions by the EMA, and relate to aspects such as impact on day-to-day life of patients. It is mentioned that they could contribute to the discussion on the acceptability of risk, but no cases of this are reported and no commenting on the benefit-risk balance is seen [26]. Involvement in BRA is thus included, but not often, it is unclear what the exact contribution is, and it is mainly on aspects not really directly addressing the benefit-risk balance.

Finally, attached to the first, second and fourth report on the interaction is a questionnaire with results on the satisfaction among patients on their involvement. In general patients are quite

satisfied with their involvement. Nevertheless, the first two reports (from 2008 and 2009, describing 2007 and 2008) show that work is being done on a reflection paper which includes the further development of procedures for patient involvement in product related issues. The reflection paper has previously been discussed and included working on a new definition on patient involvement in BRA. In the first report it is also recognized that while patients can provide valuable contributions, their opinion is usually not requested during benefit-risk evaluations. Furthermore, in the fourth report an increase in involvement in benefit-risk assessment for patients is also considered an area for improvement by the patients themselves.

Assessment documents

The EPAR summaries do not show any patient involvement. The more extensive public assessment reports show little involvement. By standard it is reported whether or not user consultation on the package leaflet has taken place. Further, a paediatric investigation plan and a risk management plan are discussed as having included patients. Overall, no involvement however in BRA is reported in these two sorts of documents. In the rules of involvement of PCO members in committee related activities (e.g. CHMP or SAG consultations) [49] it is stated that ''if the organisations' representative(s) were consulted on a centralised procedure, this consultation will be reflected in the public assessment report''. No information of patient consultation in an EPAR was however identified. Besides the EPAR's, the next set of assessment reports are the CHMP highlights. These are actually webpage's with a lot of related documents. The highlights show that patient representatives were consulted for developing measures to minimise foetal exposure to Pomalidomide, patients have been consulted on the EPAR format, and after each meeting a list of documents open for public consultation is presented. Overall, these highlights show again no involvement of patients in BRA. The final group of assessment related reports are minutes of PRAC meetings. Via the PRAC a patient member is involved in the risk assessment of drugs and consultation has taken place a couple of times. This mainly relates to measures to be taken to minimize the risk of a drug when in use. Besides the patient member (one out of about 40), consultation or participation of patients via the PRAC is limited and not related to judging benefits and risks. The assessment documents imply that patients are not consulted often on benefit-risk assessments, despite the possibilities that are available.

#	**Table 8:** findings qualitative document analysis **Main findings**
A1	No information was found in this summary on the involvement of patients and/or their views (in the assessment of Temozolomide) (like in the other EPAR summaries and reports, patient involvement in clinical trials is discussed, but this is no involvement in EMA activities and assessments).
A2	No information was found in this summary on the involvement of patients and/or their views (in the assessment of Selincro)
A3	No information was found in this summary on the involvement of patients and/or their views (in the assessment of Jetrea)
A4	No EPAR summary available for Constella
A5	No information was found in this summary on the involvement of patients and/or their views (in the assessment of Zoledronic Acid Hospira)
A6	No information was found in this summary on the involvement of patients and/or their views (in the assessment of Matever)
A7	This 47 page assessment report on Buccolam includes that patient target groups have been consulted on the package leaflet, which relates to the assessment of a drug, but not to balancing the benefits and risks, even though a leaflet can have influence on the balance in actual use. Additionally, the PDCO, which includes three patient members, has approved a paediatric investigation plan for research on the drug. Patients have thus been involved on two issues, but these cannot be considered as directly assessing benefits and risks for market approval.
A8	This document concerns a 14 page assessment report of Docetaxel Accord. Mentioned is that no user consultation has taken place on the package leaflet given the presence of a reference medicinal product for which the same leaflet is used and consultation has taken place. The report does not report of any actual involvement of patients.
A9	This is an 18 page assessment report on Zoledronic Acid Medac. Also in this report, it is mentioned that no user consultation has taken place because of the use of a package leaflet of a reference products. Further, no mentions are made of any patient involvement, be it general or specifically related to benefit-risk assessment.
A10	This 19 page assessment report on Tolucombi reports that patient groups have been consulted on the package leaflet, and that the leaflet meets the criteria for readability. Further, no mentions are made of any patient involvement, be it general or specifically related to benefit-risk assessment.
A11	This 18 page assessment reports on Voriconazole Accord reports that no consultation on the package leaflet has taken place because of the presence of a reference product with a similar package leaflet. Further, the PRAC, in which patients are represented by one member, has provided its opinion on a risk management plan. Given that the PRAC has reached their opinion by consensus and their opinion is also explained, the patient member contribution, or at least opinion is clear. Besides these two aspects, no other information on patient involvement is found. Based on this document, patients have indirectly thus been involved, although limited, and not directly in judging benefits and risks.
A12	This 67 page assessment report on Bydureon reports that target patient groups have been consulted on the package leaflet, and that this leaflet fulfils the requirements for readability. No further mentions are found of any kind of patient involvement in the assessment.
P13	The Road map to 2015 is a general policy document for the EMA which logically means that only a part can be about patient involvement. The document starts with mentioning that as a principal activity it involves patients to facilitate dialogue on issues of common interest. Relevant in the context of this study is that guiding principles in their principal activities are that the contributions of partners and stakeholders are valued, and that the EMA communicates in an open, transparent manner with all partners and stakeholders. Then, in the chapter ''Setting the scene'', involvement and participation of civil-society stakeholders, including patients, is seen as an element of growing importance. The EMA states that ''Recognising the added value of patients and consumers in benefit/risk considerations – in that they enrich regulatory decisions by complementing them with the views of those directly affected by regulatory decisions – the debate currently focuses on how to achieve more structured involvement of patients in the Agency's work''. Further, as part of the chapter on identifying drivers for change, relevant to mention is that public demands for greater transparency and openness will increase the coming years. Then, the largest chapter of the document is spend on describing how the drivers for progress and change are going to be addressed. Besides their core activities, three strategic areas have been identified for doing so; addressing public health needs, facilitating access to medicines and optimising the safe and rational use of medicines. One objective proposed, and part of the second strategic area of facilitating access to medicines, and indirectly relating to BRA, is to strengthen the involvement of patients' organisations in the

	process of preparing guidelines on medicines development. Also part of this area is that regarding the assessment process of benefit and risk it is said that ''patients' participation in healthcare decisions will further stimulate the ongoing debate on the level of patients' involvement in the scientific-review process. This should lead to patients' utilities being taken into account in a more systematic way for the benefit/risk assessment''. Additionally, also part of the second strategic area is that the EMA wants to improve the transparency of outcome of the scientific review, which means the EMA is going to cooperate with all stakeholders, including patients, on a strategy for benefit-risk assessment communication. As part of the third strategic area there are also some targets. One is to strengthen the interaction of the EMA with, among others, patient organisations in order to build up a network of excellence. Further, the EMA wants to contribute to the empowered patient concept by putting more emphasis on balanced benefit-risk communication, and ''improve the decision making process by taking due account of patient experience, thus contributing to the rational use of medicines''. Although it is not possible to say anything on the importance and the effect of patient involvement as (being) part of this framework, fact remains that patient involvement is considered in the framework. Also regarding benefit-risk assessments information is included as the EMA for instance acknowledges the growing importance of patient involvement in benefit-risk assessments, and they even think that patients' utilities should be taken into account more systematically.
P14	This policy document is a recent (last update may 2013) flyer on patient involvement at the EMA. It is stressed that the EMA will strengthen and streamline collaboration with patients, meaning they will ensure support and training, ensure efficiency of interactions, involve patients more in benefit-risk evaluations (including the PRAC), and finally ''continue to strive for high-quality information on medicines'', and involve patients in this process. The second part of the flyer consists of a listing of many of the different activities in which patients are involved; PCWP, member of diverse scientific committees, member of the MB, participation in medicines evaluation via the CHMP, participation in SAG's, participation in giving scientific advice to pharmaceutical companies, review of information, membership of networks and participating in workshops. Overall, the flyer includes policy that has been discussed in the roadmap regarding more involvement in benefit-risk assessment and better communication. Interesting is that it does not make clear what the current involvement is, but as the roadmap, the focus is on the fact that patient involvement in benefit-risk should be increased or explored.
P15	In the framework on interaction the diverse ways of involvement of patients and their organisations are described. This document from 2006 precedes the roadmap to 2015. An important point is that to contribute to the empowered patient concept two developments need to be addressed: the implementation of new community legislation and a response to other high-level initiatives. Contributing to these issues is done by achieving three objectives; providing information adapted to the patients needs, develop appropriate communication tools, and increase the awareness of patients in relation to the use of medicines. The achievement of these three objectives consists of two main parts in which cooperation should be developed. The first part is the implementation of the involvement parts of new legislation (EC No 726/2004 and Directive 2004/27/EC). The second part is about a platform of exchange between the EMA and patients; the PCWP. It is clear that the framework discusses EMA's policy on overall patient involvement. Although not explicitly mentioned, this also includes the involvement of patients in BRA, as they are for example member of certain scientific committees, and they can be consulted by SAG's. At the same time however, in 2006, there does not yet seem attention for an increase in benefit-risk as is for example the case in the roadmap to 2015.
P16	This document describes the ''Rules of involvement of members of Patients'/Consumers' and Healthcare Professionals' Organisations in Committees related activities''. Its objectives are to ''define different types of consultation, on an advisory basis, of specific Patients'/Consumers' and Healthcare Professionals' Organisation(s) on product, disease or treatment area specific issues''. This regards consultation by the scientific committees, working parties, scientific advisory groups and the rapporteurs. Interesting points made are: 1. Patients can be consulted as representative of an organisation or as a member of such an organisation but acting as an expert. 2. In the case of involvement in a product related activity, ''the agreement of the applicant/sponsor/MAH should be sought prior to disclosure of these confidential data. 3. ''In case the applicant/sponsor/MAH does not agree to a consultation with representative(s) of a Patients'/Consumers' or Healthcare Professionals' Organisation, this will be made public at the end of the evaluation procedure as part of the usual publication on outcomes (e.g. EPAR, publication on withdrawal or negative opinion).'' 4. ''Patients/consumers or healthcare professionals may be invited as an individual expert, and therefore not representing his/her organisation. He/she will have to adhere to the same rules as all other experts participating in EMEA activities, especially with regard to confidentiality undertaking....''

	5. ''If the organisations' representative(s) were consulted on a centralised procedure, this consultation will be reflected in the public assessment report (e.g. EPAR, withdrawal assessment report).''
P17	This document describes the role of patients as members of the EMA human scientific committees. The document starts with describing the legal basis of the documents and refers to the elaboration of patient involvement in the framework on interaction. Also does it refer to the advantages of patient involvement including an enrichment of the quality of regulatory decisions and an increased transparency and trust in the regulatory process. Subsequently, the document describes how many patient members are included in the scientific committees (COMP/PDCO/CAT/PRAC), and which committees do not include patient members (CHMP/HMPC). The CHMP does not include a patient representative, but it is mentioned that patients can be consulted by this committee on an ad-hoc basis, mainly on product-related issues. Although patient members act in the same way as other committee members, their role is not expected to be of a scientific nature. A list of precise tasks is defined which includes reflecting on the risk patients are prepared to take, and guarantee that scientific opinions address patient needs. Further, the document shortly describes the other roles, besides being a committee member, patients can fulfil. These are observers, experts and representatives of a patient organisation. Observers and experts must maintain confidentiality (also for patient members), while this is not the case for representatives, but for involvement of the latter the sponsor should agree before confidential data is disclosed.
P18	In this document an implementation plan for the vision in the roadmap to 2015 is described. The actions within the three strategic areas from the roadmap to 2015 are elaborated upon; addressing public health needs, facilitating access to medicines, and optimising the safe and rational use of medicines. Within the second strategic area involvement in benefit-risk assessment (possibly via utilities) and communication was identified in the roadmap, and also involvement in preparing guidelines. Regarding the latter it is mentioned that the process for guideline development should be updated to improve the interactions with stakeholders. The structure and content of the EPARs should be improved in order to improve the communication on market authorization decisions. Regarding involvement in benefit-risk assessment, this should increase in order to ensure that stakeholder views are taken into account in BRA. Within the third strategic area, optimising the safe and rational use of medicines, it is mentioned that more real-life experiences should be integrated in the benefit-risk assessment model to increase the contribution of patients in the assessments of benefit-risk. In addition, objectives regarding better communication are mentioned. For instance regarding indications of medicines and better communication on COMP decisions. Overall the documents states many objectives, but does not get much more concrete than the roadmap to 2015. An important finding is however that attention is paid to further patient involvement in benefit-risk assessment.
PR19	This document is the reflection paper on the further involvement of patients in EMA activities, dated 2009. Given the framework on interaction and the publication of two yearly reports on this (PR20 en PR21), this reflection paper describes the results on the process the EMA has engaged in with patient organisations on the further and more structured involvement of patients. It is recognized that ''in other areas where no specific legal basis exists, despite positive feedback, patient interaction and involvement still occurs sporadically for many activities in particular those related to benefit/risk considerations (e.g., ad-hoc contacts with CHMP and participation in SAGs)''. It is however recognized that patients have added value in the process of benefit-risk evaluation for the following reasons: • It would enrich regulatory outcome by complementing it with the views of those directly affected by regulatory decisions; • It would increase confidence and trust in the regulatory process; • It would lead to a higher level of transparency; • It would allow to prepare for any future integration of patients as CHMP members when foreseen in new Community legislation. Besides patient involvement in BRA, consideration should be given to the role of patients in scientific committees (P17), and the financial support provided to patients involved in

	agency activities. These three aspects/actions resulted in two proposals for action. The first is two revise the framework on interaction. This includes defining the role of patients in scientific committees and the involvement of patients in the assessment of benefit and risk. The second proposal is to provide financial support to experts and delegates. Further, the reflection paper also gives an extensive description of current involvement of patients. Some conclusions from this analysis are that patient involvement is useful and their contributions are often taken into account, patients have always participated very well (e.g. adhere to codes of conduct, sign confidentiality agreements and have been very focused in their participation). There have however also been some problems including difficulties regarding defining the precise role of patients. An important conclusion is that in 2009 it is recognized that the framework on interaction should be revised, including the role of patients in scientific committees (P17). Criteria for consultation of patient representatives and developing procedures in the areas of assessment of benefit/risk and preparation/provision of information to the public should become available, and financial support should be provided by doubling daily allowances for specific cases. Where the original framework does not, this reflection paper does (as e.g. also the roadmap to 2015) have attention for more or at least defining the role of patients in BRA.
PR20	Where the previous documents have mainly been about policy, this is the first report in a series describing the progress on the interaction with patients in relation to the framework on interaction. This first report describes the year 2007. Additionally this report presents the results of a survey testing the degree of satisfaction among patients who have been involved in 2007. Regarding the involvement of patients it is stated all actions identified in the framework have been implemented. The need for more structured and formalised involvement is however also recognized. Patients have been involved in different ways. For all activities in which patients have been involved, reference is made to the progress report, also for the other years (2008-2011). Some examples are shortly discussed. Patients have first of all been involved because of consultation by the management board. This has happened through fora such as workshops and conferences. Topics included for example "the brainstorming meeting on the provision of information by the EMEA to its stakeholders" and "the European Commission-EMEA Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC)". Secondly, patients have been consulted by the scientific committees. By the committees this has been done on specific issues of a scientific and technical nature, for example ''discussions with representatives of patients and victims of thalidomide to discuss the risk management plan for thalidomide and for Revlimid (lenalidomide)''. Via the SAG's and WP's consultation by the scientific committees has also taken place. These issues related for example to the ''disease management and the impact on the day-to-day life of the patients during the assessment of Tysabri (natalizumab)'', and the development of guidelines. Thirdly, some provisions have been made regarding public information. This for instance relates to the introduction of EPAR summaries, consultation for package leaflets and the provision of documents on some other issues. Fourthly, patients have been involved by the PCWP. The first meeting of this working party was in December 2006. Since then it has been involved on some guidelines, proposals, questions, etc. These do not seem to be related to the assessment of benefit and risk, but this cannot be stated with certainty since the PCWP has for example been involved in questions and answers on bio similar/generic medicines. On the basis of the involvement in the year 2007 two steps to be taken are identified: • ''EMEA will actively work together with the PCWP in exploring how to further develop a more systematic interaction and involvement of patients and consumers at

	different levels of the Agency's work. Particular attention will be paid to patient involvement in activities at the level of the different Committees (e.g. guideline preparation, product evaluation, etc). A Reflection Paper with proposed actions on this aspect will be developed'' (see P19). • ''The EMEA will continue to work towards the provision of high quality information adapted and oriented to patients. Patients will continue to be involved in the preparation of such information''. Overall, patients have been involved in multiple ways, following the framework on interaction. Unclear is whether certain ways of involvement really relate to BRA. Nevertheless, since patients are involved in scientific committees (which have consulted patients on issues of a technical or scientific nature), and via the SAG's patients have been consulted on issues related to disease management and the impact on the day-to-day life of the patients during the assessment of Tysabri, some relation to BRA might be assumed.
PR21	The second report on the progress on the interaction takes the same structure as the first report, but this time the year 2008 is described. For a full overview of activities reference is made to the actual reports, as is also the case for the other progress reports. First of all an increase in the number of PCOs representatives has been noticed, an increase from 77 to 165. Further, continuing from 2007 where it was mentioned that all activities were implemented, but there was a need to further formalise this, the EMA has been working on the reflection paper previously discussed. The EMA has also ''continued implementing measures aimed at improving the quality of the product related information adapted and oriented to patients''. Looking at the increase in involvement, there are again diverse activities in which patients have been involved. This relates to the management board, scientific committees (including SAG's, WP's and rapporteurs), activities related to the provision of information and the PCWP. Looking at benefit-risk there are some interesting examples, although it cannot be explained to what extent this relates to BRA. Via a SAG meeting one patient has been involved as an expert on Tysabri. Via the SAWP patients have been involved a few times in providing scientific advice. Overall most involvement does not seem to relate to the direct assessment of benefit and risk in specific cases, although patients are members of certain scientific committees, and in some cases they might have been involved in BRA. Further it is important to notice that in this and the other reports on the progress on the interaction patients are very often involved in the review of EPAR summaries and package leaflets. This involvement does not directly relate to assessing the benefit-risk balance, and does explain a big part of the increase in involvement. Finally, some next steps are identified. These include the presentation of the reflection paper and describing how to further structure patient involvement. Further, patient representatives will continue to be involved in the preparation of information meant for the public, and ''The EMEA will explore how best make patients/consumer participate in the preparation of additional EMEA information intended to the public''. The second part of the report presents again results of a questionnaire on the degree of satisfaction among those who have been involved. An area for improvement identified here is that a strategy should be developed for the further involvement of patient representatives in the work of the EMEA, and PCWP membership should be enlarged. Other areas for improvement relate to support, training and other issues.
PR22	As the second report, the third report shows an increase in number of patients that have been involvement, from 165 in 2008 to 213 in 2009. Although according to the EMA this increase can be attributed to multiple factors, which is indeed the case, by far the biggest part of the increase can be explained by an increased involvement in the review of EPARs and package leaflets. Further, report is made of the fact that the reflection paper has been endorsed by the management board, patients are involved in the review of a wider range of documents, in 2009 patients have participated in three meetings of the PhVWP as a pilot, and the PCWP has been enlarged in 2009/2010 with five patient organisation members. It is mentioned that the reflection paper contains two main proposals; revise the current framework on interaction, and provide financial support in specific cases to experts and delegates of PCO's. In the report again the specific ways in which patients have been involved are described. Looking at the judgement of benefit-risk there is first of all the involvement again of

	patient members in certain scientific committees. Additionally, by CHMP and its organs, patients have been involved in product-related issues. For example in cases of Onsenal, Prezista and Tysabri. Doubtful is to what extent this really relates to BRA. Also, in the cases that patients have been consulted on specific medicines, this often was by the EMA asking questions on paper to the eligible patient organisations. Involvement via the SAGs in 2009 was however motivation to start with a pilot phase of including patients structurally in SAG meetings. As is also mentioned in the other progress reports, patients have also been involved or consulted sometimes in or by the SAWP and PhVWP, but again exact contributions to benefit-risk assessment are unclear. Via the PCWP and information review, patients do not seem to have been involved in the assessment of benefit and risk. Looking at further steps, it is included that the framework on interaction will be revised during 2010 and 2011, ''PCOs representatives will continue to be involved in the preparation of information oriented to patients and the general public'' and the EMA will explore how this can be done best, the EMA will continue to provide further training, the role of patients in the different scientific committees will be defined (P17), and the EMA will explore involvement in benefit-risk assessment of patients.
PR23	This document is the fourth report in the series of progress reports describing the implementation of the framework on interaction, and recommendations concerning the year 2010. The total number of representatives that have been involved has increased to 307. This time the increase is because of a large increase in multiple activities (e.g. SAG meetings and SAWP consultations). Like in the previous report it is also mentioned that the scope of information review has been extended to include a wider range of documents and the PCWP and number of eligible organisations for involvement have increased. Like in all progress reports it is also stated that the framework has been implemented, but that patient involvement in BRA needs to be further explored and an increase in financial support for the patients involved is needed. Again the diverse ways of EMA bodies via which patient can and have been involved are discussed. This includes the management board, scientific committees, SAG's, SAWP, PhVWP, PCWP, review of information that should be provided to the general public, and some other activities. Relations to benefit-risk of involvement in these activities follow the same pattern again as in the previous reports. Via membership of the scientific committees patient members seem involved in the assessments, although as in the other reports no statements are made on actual contributions or precise roles fulfilled. Further, the consultation directly by the CHMP does not relate to assessing the benefit-risk balance. Consultation by the SAG's was on a number of drugs, but it is unclear what issues were addressed. SAWP consultations were on protocol assistance. By the PCWP patients have not been involved in BRA according to the activities mentioned in this document. Some next steps are also identified. First, remaining actions in the reflection paper will be implemented. Secondly, the framework on interaction will be revised during 2011/2012 including how patients and consumers can be further involved in benefit-risk assessments (implementation aim is 2012), define the specific role of patients in the scientific committees (P17), investigate how to provide further training in different areas and continue to involve PCO's in the preparation of information. Thirdly, there are some other steps; further increase the network of experts and eligible organisations in order to cover as many therapeutic areas as possible, strengthen the involvement of patients in the development of guidelines, and finally further involve patients in regulatory activities related to pharmacovigilance. Overall, for this document a similar conclusion can be drawn as for the other reports on the interaction with patients and consumers; involvement in benefit-risk assessment is included, but not extensively given the reported activities, and it is not even sure if there has been a real judgement of benefits and risks by patients. As for the first and second report, this fourth report again also includes the results on a questionnaire testing the satisfaction among patients who have been involved. Overall satisfaction is high among PCO's. A negative point is that not everybody is benefiting from financial support (only those who attends meetings).
PR24	This fifth report is the final one currently available at the EMA website. Although the content is very similar to those previously published, the main points are presented here in order to ensure nothing is forgotten. For the fourth time in a row the number of patients involved in EMA activities has increased, this time from 307 in 2010 to 423 in 2011. According to the EMA this can be explained due to ''systematic patient participation in scientific advisory group (SAG) meetings, an increased review of EMA documents, especially safety communications (Q&As) and package leaflets, and participation in new activities related to the new pharmacovigilance legislation''. Also, work has continued on the revision on the framework on interaction. The revision will focus on ''facilitating patient participation in benefit/risk deliberations, defining the role of patients involved in the scientific committees and delineating the training and support necessary to both facilitate and optimise patient involvement''. Some concrete activities have already been performed in the context of this revision.

	Patients have first of all been involved in the management board. Via the scientific committees patients have, at least indirectly, been involved in BRA because of their membership of certain committees. Looking at the CHMP, products are mentioned on which patients were involved. The CHMP has consulted patients for instance on Celexocib and Vpriv. These issues however do not concern the assessment of benefit-risk, and consultation takes place by a list of questions that have been send by the CHMP to patient organisations. Regarding the SAG's, patients have in 2011 (and partly 2010) been structurally involved in meetings. This has been useful according to the EMA, and in total 22 patients participated as experts on diverse medicines. Precise contributions and subjects of the issues addressed regarding the medicines are however not mentioned. Furthermore, on the basis of the pilot phase (see document 28) the intention is to continue with involving patients in SAG meetings. SAWP consultation has taken place 13 times, but for protocol assistance. Patients have (including the PCWP) also been consulted by the PhVWP, but it is unclear whether or not this relates to BRA. Via the PCWP patients again do not seem to be involved in benefit-risk assessment. The other activities in the report cannot be related to benefit-risk assessment. The fifth report on interaction also makes notice of the so-called VALUE (VALues and Utilities in European patients) study. With this study the EMA had four aims: • Evaluate the use of a multi-criteria decision analytic (MCDA) method to collect patient preferences • Provide quantitative data on value functions for disease outcomes within MS • Indentify the most important attributes of a treatment from the patients' perspective • Evaluate the use of the preference data as weights in an MCDA treatment decision model The study was performed in the last two months of 2011. Unfortunately, besides some general information, no specific results of this study could be retrieved. Nevertheless, one result is that preference data can be used to build decision models for actual treatments. Further use of the results of this study is thus unclear, but this is (in addition to e.g. PRAC and SAG involvement) an additional way in which the EMA seems to explore more patient involvement in benefit-risk assessment. The EMA concludes with stating that it does not expect much more increase in the number of patients involved in the coming years. Up until now the increased involvement of patients over the years ''is in line with the Agency roadmap to 2015 which emphasises that the decision-making process can be improved by taking account of patients/consumers experience''. Finally some next steps are also mentioned. This is first of all the revision of the framework on interaction including the role of patients in scientific committees (which has been concluded, see P17), a definition of patient involvement in benefit-risk assessments, and a strategy regarding the training provided to patients. Further, PCO's will continue to be involved, patient involvement in pharmacovigilance will increase (establishment of the PRAC), complete transparency on procedures for evaluating PCO's and explore how to improve the way potential conflicts of interest of organisations are handled, and finally increase the network of experts and eligible organisations.
P25	This CHMP work programme for 2011-2013 presents actions supporting the Roadmap to 2015 and its implementation plan (P13 and P18). Where these previous documents are still quite abstract, this document tries to concretise this into actions, related to those plans which are relevant for the CHMP. What this means is that the documents shows a list of objectives to be achieved by the CHMP, the responsible CHMP member and the priority given to the objective. One patient involvement related objective with high priority is the participation of civil society in SAG meetings. This includes continuing with the 1-year pilot of structural patient participation in SAG meetings, and an update of the list of questions (during procedures) for SAG's to reflect on the need for patient involvement or not. A second objective is patient involvement in benefit-risk assessments. The framework on interaction needs to be revised in order to further integrate patient values in benefit-risk assessments. A third objective is to continue with improving the EPAR's in order to inform patients and other stakeholders. These objectives are part of a list of about twenty priorities/objectives. Nineteen of them have a high priority. The involvement of patients in general and in benefit-risk is thus part of the work programme of the CHMP, but nothing new is mentioned. This latter is however logical as it is a concretisation of the roadmap to 2015 and its implementation plan. Further, the objectives have also been mentioned in the reflection paper (PR19) and the yearly reports on interaction.
P26	In this document the mandate, objectives and rules of procedure for the SAG's and ad-hoc groups are presented. SAG's function is to, on a consultative basis, provide answers to specific questions asked by the CHMP. Ad-hoc groups are meant for cases in which no specific SAG exists. The SAG's give recommendations on scientific/technical matters related to products under evaluation. Furthermore, the SAG's can by themselves also identify issues in need for further discussion, as long as the CHMP agrees. It seems that this mandate

	relates to the evaluation of benefits and risks, but it is now clear to what extent this is. Further, it seems highly likely that the SAG's do not reflect on the entire benefit-risk balance directly, but only on aspects. Specific questions are asked by the CHMP who takes the answer into account into their overall judgement. Patients can be involved in multiple ways. In general, it is mentioned that SAG's shall ''in general matters establish contacts, on an advisory basis, with parties concerned with the use of medicinal products, in particular patient organisations and health care professionals' associations relevant to the of the indication of the medicinal product concerned''. Further, patients and consumers can be appointed by the CHMP to attend SAG meetings as an expert. Also, somewhat contradictive, it is stated that if there is no patient representative as core member, one or more patient representatives will be appointed as expert. An interesting aspect is that to all participants at the meetings EMA confidentiality rules apply. The content of meetings can thus not be shared. Via SAG patients thus seem involved, also regarding benefit-risk issues, but as experts (not sharing information with their patient organisation) and only on aspects.
P27	This document is the ''CHMP workplan 2008-2010 Specialised experts and SAGs: optimisation of consultation process of CHMP''. The motivation behind the report is that given increased complexity there is a need for better and increased involvement of SAGs in evaluations. It is not clear whether the recommendations from this report are integrated in the mandate of SAG's (P26), but given the dates of the documents, this could be the case. Also given that the template for the SAG mandate looks very similar to the actual mandate (P26). A number of recommendations are given in the document in order to improve/increase the use of SAG's. One recommendation is that patient representatives could be invited to SAG meetings. On the basis of this it thus seems that the SAG's by standard include a patient as expert, and that this recommendation resulted in the pilot of one year on including patients mentioned in the reports on the interaction and the CHMP work programme for 2011-2013. Another recommendation is that the CHMP should not ask questions to SAG's that directly assess the benefit-risk balance for a product. These recommendations which all have to be carried out before the second half of 2010 make it more clear that via the SAG's patients are really involved in the assessment of medicines, either via SAG's membership or attendance as patient representative, but involvement does not mean directly assessing benefit-risk, let alone the entire balance, there is a confidentiality agreement and there is not a right to vote for patients.
PR28	This report presents the results of the one-year pilot of patient participation in SAG meetings, which is an objective of the CHMP's work programme and in which it is mentioned that a continuation of this pilot phase should take place. It is one action that explores a possible way of further involving patients in the benefit-risk assessments. The pilot phase of one year started in October 2010. By including patients the goal was to ''evaluate the contribution from the patient to the SAG meeting'', ''evaluate the impact of the overall process'' and ''serve as a basis to define the way forward''. During the pilot, patients, as the other experts, had to sign a confidentiality agreement. In total, 22 patients participated in 18 meetings. This participation was evaluated by two questionnaires, one for the patients and one for the SAG chairs and the rapporteurs. Results from the questionnaire for the SAG chairs and rapporteurs show mixed opinions. Also, both from the positive as the negative answers it turns out that patients have limits regarding the contribution they can make to technical aspects. The patients themselves evaluated the pilot phase more positive. Further it turns out from their answers also that they have limited knowledge, and that some would have liked to receive information/paperwork earlier. At the end of the document there are some final conclusions on the pilot phase. One is that involvement of patients provides increased transparency in the assessment process. Unclear is however how this has been achieved given the confidentiality agreement all meeting participants have to sign. Overall this document describes a process in which patients have been involved in benefit-risk assessments, mainly relating to risk-issues and less to efficacy issues. There is thus patient involvement in benefit-risk assessment, but as found in other documents this is low for some reasons; questions are posed in advance which means patient representatives cannot freely comment on the benefit-risk balance, exact contributions are not known because of the confidentiality agreements, the patient representatives seem limited in their knowledge and there is no commenting on the entire benefit-risk balance.

A29	This document/webpage (and A30-A34) presents so-called meeting highlights of the monthly CHMP meetings. In the highlights an overview of the adopted opinions are presented. Information related to these meetings can be found in EPAR's which have already been assessed and often some other documents, like press releases and summary of opinions. The EPAR's are not included, but the other 'first-order' related documents/webpages are also analysed for any information on patient involvement in general and in benefit-risk assessment. For all meeting highlights this amounts on average to a total of 20 to 30 documents that have been reviewed per meeting. A related press release on approval of Pomalidomide shows that patient representatives were consulted for developing measures to minimise foetal exposure to Pomalidomide. This issue is clearly related to benefits and risk, but most likely not to the evaluation of assessment of benefits and risks, and therefore not considered involvement in BRA. Additionally a list of documents open for public consultation after the meeting is published. This often relates to guidelines made by working parties. Overall, the meeting shows only involvement on risk minimisation measures.
A30	One related document is a list of documents (mainly relating to guidelines) open for public consultation after the meeting (thus not part of the meeting). Unclear is for whom this consultation process exactly is. Further, report is made of patient consultation on the EPAR format. Besides these, no other indications are found that patients or their opinions have been involved in the meeting/documents.
A31	After the meeting a list of documents open for consultation is published as has also been seen in the previous CHMP meeting highlights, but no reporting on involvement during the meeting.
A32	Again, only a list of guidelines and papers open for public consultation is published, but no reporting on involvement during the meeting.
A33	Again, only a list of guidelines and papers open for public consultation is published, but no reporting on involvement during the meeting.
A34	Again, only a list of guidelines and papers open for public consultation is published, but no reporting on involvement during the meeting.
P35	In this document the establishment and functioning of the PRAC is described. In the document it is mentioned that at that moment (June 2012) the appointment of a committee member and alternate from a patient organisation has yet to happen. Within the PRAC the alternate from a patient organisation may not act as rapporteur, while alternates from member states can. To assess whether or not patient involvement via the PRAC relates to BRA, it is needed to look at the mandate of the PRAC which relates to: ''All aspects of the risk management of the use of medicinal products including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit''. The mandate includes the assessment of risk in the context of risk management. Therefore, it is assumed the patient member can at least comment on risks or adverse effects. The tasks of the PRAC however imply that the entire benefit-risk balance is not assessed by the PRAC and no decision on this is made. This is done by the CHMP in case of centrally authorised products.
A36	This document present the minutes of the PRAC meeting of 8-11 April 2013, consisting of 79 pages. First, the PRAC includes a patient organisation member (assuming he or she has been appointed since June 2012). This means patients are involved in the risk assessments of the PRAC. Further, it is mentioned that patient consultations are/should be used for a new ophthalmology RMP, but this is for the future and has not happened as part of the meeting. Besides these two aspects no other information on patient involvement is mentioned in the many product evaluations presented in the minutes.
A37	It is unclear whether at the moment of the meeting (January 2013), a patient representative was already included in the PRAC as he/she is not present in the list of participants (document P42 shows that in November 2012 there was not yet a patient representative as member in the PRAC). Further, public consultation has taken place on the guideline on good pharmacovigilance practices (GVP) module XV on safety communication. This could mean patients have been consulted.
A38	As with the previous PRAC minutes, patient involvement in BRA can be assumed given the presence of an official patient member. The problem however is that there is not a patient member yet (at the meeting of April 2013 (A36) the list of participants shows a patient member). Besides the (not yet included) patient member, consultation has taken place on ''Standardised statements for medicinal products under additional monitoring and for the encouragement of Adverse Drug Reactions (ADR) reporting for all medicinal products''. This seems an administrative matter and not directly related to benefit-risk assessment. Finally, patients have been consulted during a workshop on summaries of risk management plans.

A39	Regarding the patient member of the PRAC, the same conclusion can be drawn as regarding document A37 and A38. Further, a patient has been invited to the PRAC meeting to present the results of PCWP's and HCPWG's joint meeting on the selection of a black symbol for products subject to additional monitoring.
P40	In this document from June 2010 the mandate, objectives and rules of procedure of the PCWP are described. The PCWP was established as part of the 2005 framework on interaction to ''adequately deal with the activities of the five EMA Human Scientific Committees''. In general the PCWP is ''established to provide recommendations to the EMA and its Human Scientific Committees on all matters of direct and indirect interest to patients in relation to medicinal products''. Although this mandate is very broad, in the document it is said that the PCWP will focus on the ''revision, implementation and monitoring of the framework on interaction''. Looking at some specific tasks, the PCWP should ''provide advice in relation to product specific matters, at the request of the EMA Human Scientific Committees'', ''liaise with other Working Parties on matters of interest to patients in relation to medicinal products'', and ''provide advice to the Co-ordination Group for Mutual Recognition & Decentralised Procedures – Human (CMD(h)) upon request, on matters of interest to patients in relation to medicinal products''. A further interesting point is that ''members who would like to bring additional participants with relevant experience for a specific topic should notify the EMA secretariat in advance of the meeting. Participation will be subject to the agreement of the Chairpersons''. Since one of the chairpersons is the EMA, the patient organisations are not completely free to invite their own experts or other participants. Furthermore, PCWP discussions are not subject to confidentiality.
P41	In this workplan of the PCWP for 2013 a schedule with meetings is given and the main issues that have to be addressed during the year. First it is stated that the PCWP is working on the revision of the framework on interaction. This revision should include a definition of the specific role of patients as members of the different scientific committees (P17), a definition of how patients are involved in the benefit-risk assessment of medicinal products, and a training strategy. Looking at the list of activities, there are many issues on which patients are involved, all not relating to the assessment of medicines. One activity also listed is the continued participation of patients in SAG meetings, but this is not a specific PCWP activity. Overall, although there is a broad mandate and the PCWP is working on a definition of involvement in benefit-risk assessment of patients, it seems that the PCWP is only used for side issues and not the real assessment of benefits and risks. In this document from January 2013, it is stated that the revised version of the framework on interaction should be presented to the management board, but no date is given.
PR42	This document presents the minutes of the PCWP meeting of 30 November 2012. Interesting is the discussion on patient/consumer involvement in benefit-risk evaluations. It is mentioned that a document has been prepared on how PCO's are and can be involved in benefit-risk evaluations. Unfortunately this document could not be retrieved for analysis. It is however mentioned that the document builds upon ''the experience of many years of involvement with the CHMP and its working parties, and also incorporates more recent experience following systematic participation of patient representatives in SAG (scientific advisory group) meetings''. Further, it is mentioned that a ''complete reflection of patients involvement in benefit/risk cannot be finalised until the PRAC is fully operational and representatives of patients have been nominated as PRAC members, as this will have an impact on the way patients will participate in benefit/risk discussions at the Agency from now on''. Both are however completed at this moment, but the reflection on the involvement in benefit-risk assessment of patients is not yet available. Very interesting is also that the PCWP was ''highlighted as the best forum to find patient and consumer expertise within a range of different therapeutic areas and could be consulted very quickly when necessary''. Documents 40 en 41 however showed that the PCWP is not much involved in benefit-risk evaluations. Overall, this document shows that patients via the PCWP are involved in multiple activities, including the development of a definition on involvement in benefit-risk assessment, but no actual involvement in benefit-risk assessment is presented.

PR43	This document also presents minutes of a PCWP meeting, albeit now those of a joint meeting with the HCPWG. The minutes show who has been involved and a short summary of each of the topics that have been discussed. What becomes clear, as also from the previous document (PR42), is that the PCWP is not participating in benefit-risk evaluations. Issues discussed are for example the participation of patients in providing scientific advice to companies for the development of medicines, and discussion and patients views on supply shortages of medicines in Europe. Although there is a broad mandate, patients are not involved in benefit-risk evaluations by means of the PCWP.
PR44	Also this document presents minutes of a PCWP meeting, those of the meeting of 30 November 2011. One interesting issue is that some patient organisations have difficulties in nominating members to participate in certain activities, especially as committee members, which is because of the new policy on conflicts of interest. This may hamper PCO's contribution to certain regulatory activities. Another issue discussed during the meeting was the implementation of the roadmap to 2015. One of the key issues highlighted during the meeting was increasing the involvement of stakeholders in benefit-risk assessment. Related is that for the year 2012 the revision of the framework is identified as a key issue to be tackled. This includes the role of patients in committees' involvement in benefit-risk assessment and the development of a strategy for training and support. Although this should be tackled during 2012, the minutes from November 2012 (PR42) show that at that moment the EMA has not made that progress. Overall, also this document shows that via the PCWP patients are involved in many issues, but not the evaluation of benefits and risks in relation to a particular medicine. Only the fact that a new definition on involvement in benefit-risk assessment should become available is discussed.
P45	Document on the functioning of the Management Board. It includes that the MB has two representatives from patient organisations as a member. Nothing is mentioned on the exact activities these two patient representatives are involved in. (But is known to be not related to benefit-risk assessment as described in the framework on interaction)

Appendix 4: Additional questionnaire results

Questionnaire respondents' involvement

Results showed that often diverse sources of information are used when the respondents are involved in BRA. These are for instance personal knowledge from living with the disease, information from the EMA, feedback from patients, information from other PCO's, literature and clinical trial data. Patient organisations do not seem to systematically consult members/patients or send them surveys.

The use of patient preferences

The possible use of patient preferences/stated preference methods was addressed by assessing when to use preferences, who should collect them, in which cases to use them and the motivation of patients to personally use preferences. The following four figures/tables present the results on these questions.

Table 9 – The moment to use preferences (N = 37)	n (%)[A]
Before submitting an application for authorisation: in pre-clinical research	9 (24)
Before submitting an application for authorisation: in the ethics committees	14 (38)
In the initial marketing authorisation application (submitted by the sponsor)	10 (27)
During the authorisation procedure (after the initial application, but before a decision is reached)	17 (46)
After the market authorisation (for instance when pharmacovigilance activities show a higher risk profile than expected during the authorisation)	14 (38)
During the authorisation procedure, but not necessarily in an application as part of scientific committee discussions, they should only be used by patient organisations at the moment considered appropriate (e.g. in consultation by the scientific committees, SAG's or WP's)	8 (22)
During the authorisation procedure, but not always in an application as part of scientific committee discussions, they should only be used by the scientific committees at the moment considered appropriate	3 (8)
Do not know	3 (8)
Other	7 (19)

[A] Respondents were able to select multiple answers; therefore, the total exceeds 100%

In addition to the results in table 9 some respondents are sceptical and think that preferences should for instance only be used in special cases (e.g. very high risk of adverse effects).

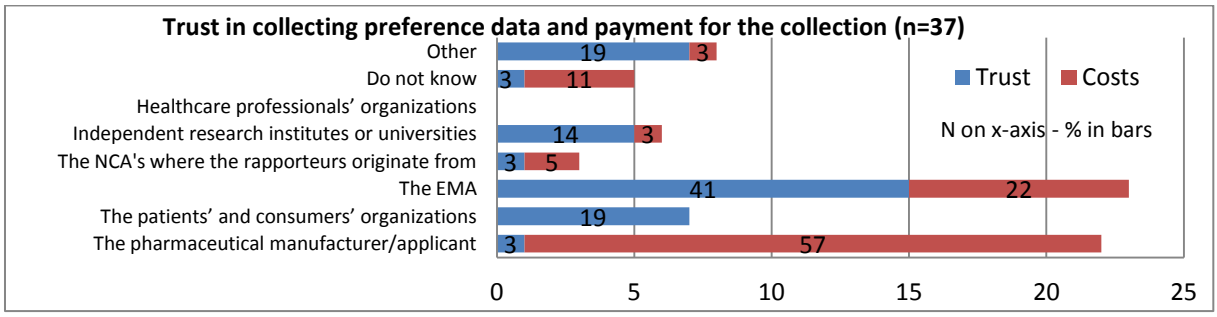


Figure 3: collection of the preference data

Figure 3 shows that the EMA is trusted most for collecting the data. The pharmaceutical manufacturer should however pay for the collection. A comment from the questionnaire is that many research institutes might apply for the data generation because of the money it generates. Of the respondents who indicated 'another', five of them want the EMA to collect the data, raising the total to 20.

Table 10 – The cases in which it is important to consider patient preferences (N = 37)	n (%) [A]
High benefits, relative high risk for multiple minor adverse effects	13 (35)
High benefits, relative high risk for a fatal adverse effect	16 (43)
Low benefits, relative low risk for minor adverse effects	4 (11)
Low benefits, relative low risk for a fatal adverse effect	10 (27)
In the case of a new medicine in a area of unmet medical need (current medicines are not sufficient)	13 (35)
In the case of a new medicine in a area of unmet medical need (there is no current medicine)	14 (38)
In the case of a new medicine for rare diseases	16 (43)
When evidence is mainly about benefits and risks for a particular group (e.g. age 30 to 50), but when approval is sought for a wider or other audience than that particular group	12 (32)
In the case that there is relative much uncertainty surrounding the data on benefits and risks of a medicine	15 (41)
Always	12 (32)
Never	3 (8)
Do not know	1 (3)

[A] Respondents were able to select multiple answers; therefore, the total exceeds 100%

This study shows (table 10) that patient preferences can be used in all cases according to the respondents, although almost nobody wants to use them when benefits and the risk for minor adverse effects are low.

Table 11 - Motivation of patients to personally use preferences in BRA (N = 37)	mean (SD)[D]
Expectancy	0.53 (0.23)
Instrumentality	0.6 (0.25)
Valence	0.45 (0.72)
Motivational force c	**0.21 (0.28)**

[D] Does not equal to multiplying E, I and V since motivational force was calculated as the average (mean) force of the 37 respondents, not as a result of multiplying the averages of E, I and V.

The fourth aspect concerned patients' motivation to personally apply preference data when for example being consulted or being a member of a scientific committee or advisory group. Expectancy and instrumentality are scores on a scale from 0 to 1, and valence on a scale between -1 and 1. The scores are respectively 0.53, 0.6 and 0.45. These scores are neither high nor low, meaning patients to some extent think they can handle preferences, believe that preferences contribute and believe the patients view contribution is important. Calculating the overall motivation of respondents, a score of 0.21 was obtained, which should be interpreted on a scale of -1 to 1, Since only one performance level was considered (a 'high level'), the motivation can only be related to this.

The possible value of patient preferences

To assess the possible value of patient preferences, the respondents scored the current situation (no use of preferences) and a hypothetical situation in which preferences could also be used. The difference was taken as the added value of patient preferences. Only on transparency a significant difference was observed.

Given that only on the criterion of transparency a significant difference was observed it was interesting to look at the composition of the average scores (table 12). For all criteria almost half or more of the respondents gave the same scores to both the current situation as the hypothetical situation of also using preferences, meaning they do not think any situation is better or worse than the other.

Table 12 - The value of using preferences - negative, equal and positive scores

Criterion	Score current situation higher n (%)	Equal score n (%)	Score higher with preferences n (%)
Representativeness	9 (24%)	18 (49%)	10 (27%)
Early involvement	8 (22%)	23 (62%)	6 (16%)
Influence 1	5 (14%)	26 (70%)	6 (16%)
Influence 2	4 (11%)	26 (70%)	7 (19%)
Transparency	3 (8%)	19 (51%)	15 (41%)
Sure of myself (DCS 1)	9 (24%)	17 (46%)	11 (30%)
Understand information (DCS 2)	8 (22%)	20 (54%)	9 (24%)
Risk-benefit ratio (DCS 3)	6 (16%)	24 (65%)	7 (19%)
Encouragement (DCS 4)	6 (16%)	20 (54%)	11 (30%)

Besides assessing the differences on the criteria, subgroup analysis was used to assess possible differences in scores between groups based on the level of involvement and whether or not their involvement allows them to provide input in BRA. For the first categorization the Kolmogorov-Smirnov test was used to compare two groups (consultation and participation). For the categorization on the basis of involvement in BRA (four groups) the Kruskal-Wallis test was used, and when significance was found pair-wise comparison with the Mann-Whitney U test was applied. Finally, for comparing the same groups between the two measurements instead of the different groups within one measurement, the Wilcoxon signed rank test was used again.

A few significant results were found, but these did not provide information useful for the paper. By using the factor (sub group variable) whether or not participants' involvement allows them to provide input when involved in BRA, a few significant results were found. By comparing groups on the outcome criterion 'influence 1'' for the current situation a significant difference was found between groups using the Kruskal-Wallis test (χ^2 (3, N=37)=9.4; P=0.024). Table 13 shows that those who are not allowed to provide input in benefit-risk gave a lower score for the current situation than those who are allowed to do so and those who do not know. Further pair wise comparison using Mann-Whitney-U shows the significant difference is only between these two ('Do not know' and 'No') (U=9, Z=-2.53, P=0.017) (exact 2-tailed, corrected for ties).

Table 13 - score on criterion 'influence 1' for the current situation by subgroup variable providing input in BRA or not

Subgroup	Mean(SD)
Yes, on the entire benefit-risk balance	3.8 (0.2)
Yes, but only on aspects of the benefit-risk balance	3.2 (0.29)
No	2.8 (0.32)
Do not know	4.0 (0.2)

Table 14 - score on criterion ''influence 2' for the hypothetical situation of additionally using preferences by subgroup variable providing input in BRA or not

Subgroup	Mean (SD)
Yes, on the entire benefit-risk balance	4.0 (0.26)
Yes, but only on aspects of the benefit-risk balance	3.0 (0.26)
No	2.9 (0.35)
Do not know	3.7 (0.29)

By comparing the outcome criterion 'influence 2' for the situation in which preferences are also available for involvement in BRA, a significant difference was found between groups using the Kruskal-Wallis test (χ^2 (3, N=37)=8,1; P=0.043). Table 14 shows that those who are allowed to provide input on entire benefit-risk balance give a higher score than those who not are allowed to provide input and those who are allowed to do so only on aspects of the benefit-risk balance. Pair wise

comparison using Mann-Whitney-U shows a significant difference between 'The entire benefit-risk balance' and 'Only on aspects' is (U=21, Z=-2.3, P=0.029) (exact 2-tailed, corrected for ties), and between 'The entire benefit-risk balance' and 'No' is (U=19.5, Z=-2.18, P=0.029) (exact 2-tailed, corrected for ties).

Measures to facilitate the use of patient preferences

For the possible changes needed to facilitate the use of patient preferences, results where categorized into three groups, already presented in the paper.

Questionnaire drop-outs

Besides the four parts of which the questionnaire consisted and of which additional results are presented in this appendix, a short look was also taken at the non-respondents. Besides the 37 respondents, 34 others started with the questionnaire, but did not complete it. In table 15 the moments at which they dropped out are presented. No particular reason can be appointed why the drop-outs did not complete the questionnaire.

Table 15 - Questionnaire drop-outs (N=34)

Moment of stopping	N (%)
First part (on their own current involvement, question 1-5)	20[E] (59%)
Second part (process aspects, question 6-12) - did not fill in any question here	9 (26%)
Question 13 - on checking validity of the outcome criteria	1 (3%)
Question 14 - criteria for current involvement	1 (3%)
Question 15 - criteria when also using preferences	1 (3%)
Completed fully, but no submission	2 (6%)

[E] 3 out of 20 completed one or a few questions, but the others did not fill in any question