Title:

Economic considerations and patients' preferences affect treatment selection for rheumatoid arthritis patients: A discrete choice experiment among European rheumatologists

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Abstract

Objective:

To compare the value that rheumatologists across Europe attach to patients' preferences and economic aspects when choosing treatments for rheumatoid arthritis (RA) patients.

Methods:

In a discrete choice experiment European rheumatologists chose between two hypothetical drug treatments for a patient with moderate disease activity. Treatments differed in five attributes: efficacy (improvement and achieved state on disease activity), safety (probability of serious adverse events), patient's preference (level of agreement), medication costs and cost-effectiveness (incremental cost-effectiveness ratio (ICER)). A Bayesian efficient design defined fourteen choice sets and a random parameter logit model was used to estimate relative preferences for rheumatologists across countries. Cluster analyses and latent class models were applied to understand preference patterns across countries and among individual rheumatologists.

Results:

Responses of 559 rheumatologists from 12 European countries were included in the analysis (49% females, mean age 48 years). In all countries, efficacy dominated treatment decisions followed by economic considerations and patients´ preferences. Across countries, rheumatologists avoided selecting a treatment that patients disliked. Latent class models revealed four respondent profiles: one traded off all attributes except safety, and the remaining three classes disregarded ICER. Among individual rheumatologists, 57% disregarded ICER and these were more likely from Italy, Romania, Portugal or France whereas 43% disregarded uncommon/rare side effects and were more likely from Belgium, Germany, Hungary, Netherlands, Norway, Spain, Sweden or United Kingdom

Conclusion:

Overall, European rheumatologists are willing to trade between treatment efficacy, patients' treatment preferences and economic considerations. However, the degree of trade-off differs between countries and among individuals.

Background

Traditionally, drug treatment decisions for patients with rheumatoid arthritis (RA) were primarily based on benefits and risks associated with a drug. Patient´s preferences and treatment costs usually received little attention, only [1]. The introduction of biologics has increased treatment opportunities substantially. The new treatments are between 20 and 60 times more costly, and therefore raise concerns about affordability of RA care [2, 3]. Today, in most European countries, access to biologics is highly regulated [4] . In addition to the economic dimension becoming increasingly important, physicians across Europe are encouraged to actively involve their patients in treatment decisions. Patient-centered-care is expected to improve adherence to agreed treatment plans and thus positively influence health outcomes [5]. However it can be a challenge to include patients´ preferences in decisions that are influenced by multiple other aspects.

Although costs and cost-effectiveness (CE) have been given consideration in recent European League Against Rheumatism (EULAR) developed treatment recommendations [6, 7] recommendations rely mainly on evidence for effectiveness and safety. Optimal patient care across Europe will depend on how recommendations are implemented in the context of differences in the economic situations of countries and differences in the attitudes of physicians and patients. A recent article revealed a strong association between access to (expensive) biologics and the country´s wealth [8]. Interestingly however, another review found that drug coverage for innovative and expensive drugs does not necessarily translate into its use; there were differences in use between countries with comparable reimbursement criteria, and also between regions within a country [9]. Differences in attitudes among clinicians likely contribute to differences in treatment choices [10].

To our knowledge, limited data exists about the differences in values that rheumatologists attach to various treatment characteristics beyond efficacy and safety. Little is known about how rheumatologists assess economic consequences of a treatment choice – do they take into account relative CE considerations or primarily use absolute costs to make economic trade-offs? Moreover, there is limited research on how rheumatologists consider patient´s preferences.

In this study, we aim to assess if rheumatologists across Europe are willing to trade-off treatment efficacy and safety for economic considerations and patients´ preferences. Further, the study aims to determine different preference profiles of rheumatologists and whether preference profiles are associated with the country rheumatologists are located in.

Methods

A discrete choice experiment (DCE) was designed to investigate relative preferences of rheumatologists when choosing drug treatments in RA. In the DCE, rheumatologists were presented with a series of choices and asked in each to select the preferred drug treatment among two hypothetical treatment options (A or B). The treatment options were described by a set of attributes, further specified by attribute levels.

Selection of Attributes and Levels and Patient Profile

Selection of attributes and levels is fundamental in the design of a reliable DCE study [11, 12]. We followed a step wise approach. First, potentially important attributes, attribute definitions and levels were identified from literature [11, 13-23]. Second, an expert group (n=6) consisting of rheumatologists and experts in the field of economic evaluations, DCE and decision-making agreed on an initial list of attributes/definitions/levels. Third, the proposed candidate attributes/definitions/levels were discussed with 8 rheumatologists from three countries to ensure they reflected clinical realities.

Five attributes were selected for the DCE: efficacy (status and improvement of disease activity score of 28 joints (DAS28), safety (risk of a serious adverse event (AE)), patient´ s preference (level of agreement with treatment choice), annual drug costs and CE (Incremental Cost-effectiveness Ratio (ICER) compared to usual care expressed as incremental cost of one quality adjusted life year (QALY) gain)). For each attribute, three levels were agreed (figure 1).

The patient profile (possibly influencing treatment choices) was selected to imply a clear need for change in the treatment and a decisional problem in terms of balancing previously agreed attributes. The patient profile allowed for a switch to expensive (biological) medications in the majority of countries to ensure respondents do not feel intuitively restricted in their decision by local health care regulations. The agreed profile described a patient with anti-citrulline antibody positive RA and moderate disease activity despite two conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs). The full patient profile (*online supplementary table S1)* has been approved by experts and rheumatologists

Experimental design

Based on the attributes and levels there are 243 (3^5) possible treatment combinations - too many to ask each rheumatologist to evaluate [24]. We reduce the number of choice sets using a Bayesian efficient experimental design (Ngene software [25]). A Bayesian design aims to maximize precision of estimated parameters for a given number of choice questions [26] by incorporating *a priori* information about sign and value of parameters. The *a priori* information was gained from a preliminary DCE with 10 rheumatologists. Implausible or unrealistic treatment options were excluded from the design (e.g. efficacy

is low, costs are high, but the CE is best). In addition three choice sets were included to test if respondents made sensible choices. 1. a dominance test – a choice set with one treatment option that is clearly better the other; and 2. two repeated choices – choice sets that repeat earlier choices to assess the stability of respondents´ choices. A total of 17 choice sets were included in the questionnaire. An example of a choice set is shown in figure 1.

The questionnaire

The questionnaire consisted of two parts – 1. the DCE task and 2. questions collecting socio-demographic data (e.g. age, gender, work environment) to facilitate interpretation of the results. The full questionnaire was piloted among rheumatologists (n=14) from two different countries to ensure that choice sets, attributes and levels were relevant, clear and plausible across countries. Economic attributes were presented in local currencies [27]. An online survey was distributed by email through a national principle investigator (PI) per country.

Country selection

As attitudes of rheumatologists may be influenced by external factors like the country´s culture, wealth or health care environment, countries from all geographic regions in Europe were invited: Belgium (BE), France (FR); Germany (GE), Hungary (HU), Italy (IT), Netherlands (NL) Norway (NO), Portugal (PT), Romania (RO), Spain (SP), Sweden (SE) and United Kingdom (UK).

Statistical analysis

A rheumatologists responses were considered for data analyses when at least 50% of choice sets were completed and they successfully passed the dominance test. A three-step approach was used to analyse data.

First, a mixed logit (ML) model was used to assess the relative importance of attributes, using Nlogit, version 5 [28]. The following utility model was estimated:

$U_{ij} = \beta 0 + (\beta_1 + \eta_{1i})$ *Good response* $+ (\beta_2 + \eta_{2i})$ *Remission* $+ (\beta_3 + \eta_{3i})$ *Rare AE* $+$
$(\beta_4 + \eta_{4i})$ *Uncommon AE* $+ (\beta_5 + \eta_{5i})$ *Favoured preference* $+ (\beta_6 + \eta_{6i})$ *Disfavoured preference* $+$

$(\beta_7 + \eta_{7i})$ *Cost-effectiveness* $+ (\beta_8 + \eta_{8i})$ *Costs*

U represents the observable relative preference of rheumatologist (i) for a treatment choice (j) which can be defined as a sum of preference scores for attributes/levels. β_0 is the constant, $\beta_{1\text{-}8}$ are the mean attribute utility weights (physician's preferences) for the respective attribute and η_i represents the random parameter for rheumatologist i. Dummy coding was used to describe variables $\beta_{1\text{-}6}$. Reference categories

for efficacy, safety and patient´s preference were moderate response, very rare adverse events and neutral patient attitude, respectively. The signs of the β coefficients indicate whether the attribute has a negative or positive effect on the rheumatologists' preference. A ML model allows model parameters to vary between respondents, which is reflected in the random parameter. If the standard deviation (SD) of this random parameter is significantly different from zero, this is interpreted as evidence of significant preference variation for the attribute within the population [29]. Results were considered significant for $p<0.05$.

The relative importance of attributes was calculated based on the range of the level coefficients per attribute. using the method described by Malhotra and Birks [30]. More specifically, the relative importance weights were derived by dividing the range of the level coefficients for one attribute by the sum of ranges of coefficients of all attributes.

Second, to assess potential similarities, countries were grouped on the basis of their similarity in mean relative importance weights across the five attributes. Hierarchical Ward´s linkage with a squared Euclidean distance measure was used (using STATA version 12 [31]). To determine the optimal cluster number, a second clustering method (k-means) was applied and results were compared to hierarchical Ward´s linkage to verify if cluster structures were reproducible. Introduction of additional clusters was stopped where both clustering methods provided different results. Further we based the decision on numbers of clusters on the rule of thumb suggesting $k \sim \sqrt{(n/2)}$, with k describing the number of suggested clusters and the number of observations.

Third, a latent class model (LCM, using Nlogit) was used to determine preference profiles of all individual rheumatologists. LCM can be used to identify the existence of and the number of classes in the population based on their treatment preferences. The LCM can also be used to explore if covariates (such as clusters of countries) influence the probability to belong to a particular class. Class membership is latent in that each respondent belongs to each class up to a modelled probability [32]. In order to determine the number of classes, we selected the model with the best fit based on the Akaike information criterion. To further understand the role of country, previously developed country clusters were added as covariate to the latent class model in an additional step. Statistically significant parameter estimates ($p<0.05$) indicate that the covariate (i.e. the dummy of country-cluster) contributes to the explanation of latent classes. For example, if the parameter estimate for the covariate "country cluster" is positive and significant for a certain class, it indicates that rheumatologists from the countries that belong to the country cluster are more likely to belong to that particular class.

Results

Respondent's socio-demographic characteristics

Overall 559 rheumatologists from 12 European countries were included in the analysis. Mean age was 48.0 years and 49% of rheumatologists were females (table 1). Test- retest reliability was in line with existing literature [29] with 82.3% (re-test 1) and 80.8% (re-test 2) of respondents having chosen the same alternative in the test–retests. Five respondents failed in the dominance test and were therefore excluded from the analysis.

Attribute preferences when selecting a new treatment, overall and at a country-level

The main results of the MLmodel are summarized in table 2a (coefficients) and 2b (relative importance) for all countries and each country separately. The detailed results overall and per country from ML models can be extracted from *online supplementary table S2*.

Coefficients (table 2a) revealed, that in all countries good response and especially remission were significantly more desirable than moderate response ($\beta_{remission} > \beta_{good\ response}$). When coefficients were significant, probability of a serious adverse event decreased preference for that given treatment option ($\beta_{uncommon} < \beta_{rare}$). The patient´s agreement with the treatment was universally associated with an increased preference and a stronger, negative impact on preference was seen when patients dislike treatments ($|\beta_{disagreement}| > |\beta_{agreement}|$).The contribution of patient´s disagreement with a treatment choice was significant in all countries. The economic aspect also played an important role. Higher economic burden was consistently associated with decreased preference. CE was not significant in three countries (FR, IT, RO), medication costs however were significant in all countries.

When comparing contribution of different attributes across countries (table 2b), results revealed that efficacy dominated the treatment choice in all countries with comparatively low variations between countries (range 39-52%). High variability was observed for the relative contribution of safety (range 1-20%) whereas patient´s preference played role in all countries (range 7-21%). Similarly, absolute costs played a role in all countries (range10-24%) whereas contribution of CE varied importantly with several countries largely disregarding CE (range 4-21%). In the majority of countries absolute costs were more important than relative CE considerations.

Cluster of countries according to the preference profile

Two clusters were identified (table 2). In cluster 1 (BE, GE, HU, NL, NO, SE, SP, UK) all attributes, except safety, had a relevant contribution to treatments choice. In cluster 2 including (FR, IT, PT RO), there was a higher emphasis on safety (range 18-20%) and lower emphasis on relative CE considerations (range 3-8 %).

Classes of individual rheumatologists according to the preference profile

Four classes of rheumatologists have been identified according to their preference profile (table 3).In all classes, efficacy (both levels) and patient´s disagreement with a treatment were significant determinants of treatment choice. In class 1, rheumatologists accounted for both economic attributes (absolute costs and relative CE) but largely disregarded safety. Overall, 43% of rheumatologists were estimated to belong to class 1. Rheumatologists belonging to one of the remaining classes 2-4 disregarded ICER. Respondents of class 3 balanced safety and total medication costs, while those in class 2 and 4 accounted only for either safety (class 2) or total medication costs (class 4)
. The probabilities to belong to classes 2, 3 and 4 were estimated with 22.6%, 31.1% and 11.1% respectively. Rheumatologists from country cluster 2 (FR, IT, PT RO) were significantly more likely to be located in classes 2, 3 and 4, with CE playing a minor role.

Discussion

The study revealed that across countries rheumatologists are willing to trade-off efficacy against patients´ preferences and/or economic aspects in treatment choices. 43% of rheumatologists balanced all attributes, including CE when choosing a therapy, while for all other rheumatologists, CE did not play a substantial role. Medication costs however remained relevant for 77% of clinicians. Two groups of countries could be distinguished. One group, which represented the majority of countries, was more likely to balance all treatment attributes including CE, while the other group placed little emphasis on CE.

In all countries, rheumatologists considered economic, indicating that rheumatologists support efficient use of limited health care resources. However, latent class analyses showed that about half of individual rheumatologists are estimated to largely disregard the CE. This can be explained by clinicians having limited access to CE data of relevant drugs or methodological complexities and weaknesses in existing data [33, 34]. Given the importance of ICER, we need to ensure that trustful and comparable good quality data are provided to clinicians to support its use in clinical decision making. In addition, the direct health care environment often rather supports economic trade-offs based on absolute costs [35] even though CE data provide more valuable information on efficient treatment choices for society. The present findings confirmed that in UK CE and more specifically ICER plays a more decisive role in reimbursement decisions compared to many other European countries [36].Of note, CE studies are frequently limited to

selected countries although transferability of data across countries is not always possible, further limiting its use [33].

Patients´ preferences were taken into account by all rheumatologists, despite variations observed among individuals and between countries. Cultural differences in the physician-patient relationship or the physician´s attitude may partly explain the differences. A recent review e.g. found that clinicians are more likely to support shared-decision making when their direct work environment supports the concept [1]. Interestingly however, rheumatologists from all countries considered in particular patient´s disagreement, possibly to avoid poor drug adherence. Although perception towards shared decision making can vary, this study for the first time revealed consensus among individuals and across countries on the importance of a patient´s disagreement, and is the first to address patient´s preferences in the context of other treatment attributes.

Some limitations have to be considered for interpretation of results. First, the sample size was lower in some countries and differences in socio-demographics across countries were observed, thus selection bias and limitations in generalizability of results cannot be excluded. Sub-group analyses of the results from NL (results not reported), revealed no significant differences in preferences for different sub-groups. Further an efficient experimental design was developed to optimize response efficiency. Second, pharmaceutical industry [37] or local health care regulations (in particular the reimbursement criteria) may influence the preferences. However, most participating countries do not restrict access to expensive drugs for patients described in the DCE, therefore this type of effect is likely limited to countries with very strict criteria (UK, HU and RO). Third, although the presented attributes were confirmed as most relevant for treatment decisions in RA and a strong methodology was used to select and defined attributes, it cannot be excluded that further attributes play a role in some countries. Further research could contribute to a better understanding on other relevant factors across European countries. Fourth, presenting two economic attributes – costs and CE - in the DCE has it´s limitation as also absolute costs together with efficacy and safety provide insights into CE of a drug. However, only including both economic attributes allowed to raise awareness on the fact that clinicians are still predominantly focused on costs.

Finally, this study provides only insight into stated preferences. It remains unknown whether rheumatologists reach decisions in the same way in clinical practice as they state in the theoretical framework of the DCE. Also, in clinical reality however decisional problems may exceed the complexity reflected in the study design. Revealed preferences would be additionally informative, however design and execution of such a study would be very difficult.

Despite limitations, this study reveals that values rheumatologists attach to treatment characteristics vary importantly between countries and among individual rheumatologists. The complexity of today´s treatment decisions justifies more research on behavior of prescribers, as the clinicians' attitude is one important factor contributing to quality and equality in healthcare. We hope the current study will raise awareness on the importance of physicians' behaviors and open discussion on how clinicians are expected to trade-off various aspects of a treatment decision.

Conclusion

Overall, rheumatologists take efforts to balance multiple aspects of a treatment choice including the patient´s potential disagreement and the economic consequences. However important differences in the assessment of economic aspects were observed between and within countries. In most countries clinicians still focus on absolute costs while CE would provide more valuable information on the societal consequences of a decision.

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Ethical approval information

The survey included clinical personnel (rheumatologists) only, ethical approval was not required for this type of study.

Author disclosure statement

Monika Hifinger contributed during an unpaid extended maternity leave (2013-2016) agreed with Hexal AG, Germany. Related to the topic of this study, all other co-authors have no disclosures to declare.

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Tables and Figures

Table 1: Characteristics of rheumatologists for the total group and each country separately

		Gender	Age	Work environment
		$n_{female}/n_{overall}$ (% female)	years ± SD	$n_{academic}/n_{overall}$ (%) academic setting
Belgium	(n=33)	16/32 (53%)	41.4 ± 8.0	16/32 (53%)
France	(n=40)	21/38 (55%)	51.7 ± 10.6	2/38 (5%)
Germany	(n=44)	16/43 (37%)	49.3 ± 8.9	8/43 (19%)
Hungary	(n=71)	48/70 (69%)	50.6 ± 11.1	34/70 (49%)
Italy	(n=59)	20/57 (35%)	44.0 ± 11.4	31/57 (54%)
Netherlands	(n=63)	28/63 (44%)	48.9 ± 7.6	21/63 (33%)
Norway	(n=41)	22/39 (56%)	47.6 ± 10.2	17/39 (44%)
Portugal	(n=39)	19/36 (53%)	46.7 ± 12.8	11/36 (31%)
Romania	(n=42)	25/42 (59%)	43.3 ± 9.2	20/42 (48%)
Sweden	(n=24)	16/24 (67%)	50.5 ± 9.7	18/24 (75%)
Spain	(n=63)	31/62 (50%)	48.1 ± 8.3	54/62 (87%)
United Kingdom	(n=40)	9/40 (23%)	53.5 ± 8.1	34/40 (85%)
All countries	(n=559)	267/546 (49%)	48.0 ± 10.1	266/546 (49 %)

N= number of responses, SD= standard deviation

Figure 1: Attributes and levels and example choice set of DCE experiment

(a) Attributes and levels describing drug treatment options in DCE experiment

ATTRIBUTES AND ATTRIBUTE DEFINITIONS	ATTRIBUTE LEVELS	LEVEL DESCRIPTIONS
Efficacy **Improvement and status of disease activity based on DAS28*	1. Good DAS28 response – remission achieved	DAS28 improvement by 3.0 points Achievement of remission (DAS28<2.6)
	2. Good DAS 28 response – low disease activity achieved	DAS28 improvement by 2.0 points Achievement of low disease activity (2.6<DAS28≤ 3.2)
	3. Moderate DAS28 response	DAS28 improvement by 1.0 point Low disease activity or remission cannot be achieved (DAS28 remains >3.2)
Safety *Probability of a serious adverse event*	1. Very rare 2. Rare 3. Uncommon	5 out of 100,000 patients 5 out of 10,000 patients 5 out of 1,000 patients
Patient´s Preference *patient expressed level of agreement with treatment choice*	1. Treatment favoured 2. Neutral 3. Treatment disfavoured	
Cost-effectiveness ** ICER, *in costs per QALY gained*	1. Favourable 2. Moderate 3. Unfavourable	15,000 €/QALY 30,000 €/QALY 75,000 €/QALY
Overall medication costs *Per year, in local currency*	1. Low 2. Medium 3. High	800 EUR/year 8,000 EUR/year 14,000 EUR//year

(b) Example choice set - repeated 17 times with varying attribute levels

EXAMPLE CHOICE SET	TREATMENT A	TREATMENT B
Improvement of DAS28 disease activity	**Good response – Low disease activity achieved** DAS28 improved from 4.6 to 2.6 · SCJ improved from 5 to 2 · TJC improved from 5 to 2 · ESR improved from 18 to 4 · PGA improved from 49 to 29	**Good response – remission achieved** DAS28 improved from 4.6 to 1.6 · SCJ improved from 5 to 1 · TJC improved from 5 to 1 · ESR improved from 18 to 2 · PGA improved from 49 to 19
Risk of serious adverse events	**Rare –** 5 patients out of 10,000 patients	**Uncommon –** 5 patients out of 1,000 patients
Patient´s preference	The **patient disfavours** treatment	The **patient favours** treatment
Cost-effectiveness	**Unfavourable –** 75,000 EUR/QALY	**Moderate –** 30,000 EUR/QALY
Medication costs	**High –** 14,000 EUR/year	**High –** 14,000 EUR/year
Which treatment would you choose for the patient?	**Treatment A**	**Treatment B** X
In the example choice set the respondent preferred treatment B over treatment A when choosing a drug treatment for a patient with moderate disease activity		

DCE=discrete choice experiment, DAS28=disease activity core 28; ICER =incremental cost effectiveness ratio, QALY=quality-adjusted life year
***** In the choice sets, also changes of the individual DAS28 components (tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), patient global assessment of disease activity (PGA)) were presented → see figure 1
****** ICER is expressed in costs (€) per QALY gained for the selected treatment compared to usual care

Table 2: Results from the Discrete Choice Experiment

a) Results from the Random Parameters Logit Model (β coefficients per attribute level reflecting physician's preferences for the respective attribute)

Country/N / Treatment Attribute/Level	BE 33	NO 41	GE 44	SE 24	NL 63	UK 40	HU 71	SP 63	FR 40	IT 59	PT 39	RO 42	All countries 559
Efficacy													
Moderate response	Reference level (efficacy)												
Good response	**2.08*** **	**2.93*** **	**2.93*** **	**2.81*** **	**2.40*** **	**1.92*** **	**2.31*** **	**3.33*** **	**2.49*** **	**2.41*** **	**3.40*** **	**4.96*** **	**2.30*** **
Remission	**3.55*** **	**4.32*** **	**5.44*** **	**5.05*** **	**4.40*** **	**3.47*** **	**4.34*** **	**5.35*** **	**3.90*** **	**4.66*** **	**5.07*** **	**8.86*** **	**3.91*** **
Safety													
Very rare	Reference level (safety)												
Rare	-0.37	-0.30	**-0.65** **	**-0.82** **	0.14	0.00	**-0.41** **	-0.16	**-0.61*** **	**-0.89*** **	**-1.14*** **	**-1.15** **	**-0.41*** **
Uncommon	**-0.97*** **	**-1.04*** **	**-1.21*** **	**-1.28*** **	0.05	-0.19	**-1.13*** **	**-1.13*** **	**-1.78*** **	**-1.75*** **	**-2.49*** **	**-3.31*** **	**-1.04*** **
Patient´s preference													
Patient favours treatment	0.17	0.24	**0.57** **	0.47	0.29*	**0.44** **	**0.62** **	**0.71*** **	**0.53** **	**0.49*** **	0.00	0.04	**0.40*** **
Patient is neutral	Reference level (patient´s preference)												
Patient disfavours treatment	**-0.84*** **	**-1.27*** **	**-1.28*** **	**-1.75*** **	**-1.45*** **	**-1.22*** **	**-0.87*** **	**-1.44*** **	**-1.40*** **	**-0.97*** **	**-1.69*** **	**-1.12** **	**-1.03*** **
Cost-effectiveness (10,000 EUR/QALY)	**-0.15*** **	**-0.21*** **	**-0.03*** **	**-0.19*** **	**-0.23*** **	**-0.31*** **	**-0.22*** **	**-0.21*** **	-0.05	-0.14	**-0.18** **	-0.11	**-0.15*** **
Overall medication costs (1,000 EUR/year)	**-0.12*** **	**-0.19*** **	**-0.19*** **	**-0.15*** **	**-0.18*** **	**-0.14*** **	**-0.09*** **	**-0.16*** **	**-0.09*** **	**-0.12*** **	**-0.19*** **	**-0.23*** **	**-0.12*** **
Constant	0.14	-0.15	**-0.40** **	-0.30	**-0.26** **	**-0.32** **	**-0.15**	0.02	-0.16	**-0.31** **	-0.24	-0.57	**-0.15*** **
McFadden Pseudo R-squared (R2).	0.61	0.65	0.66	0.67	0.46	0.63	0.63	0.65	0.58	0.63	0.64	0.63	0.39

BE=Belgium, FR=France, GE=Germany, HU=Hungary, IT=Italy, NL=Netherlands, NO=Norway, PT=Portugal, RO=Romania, SE=Sweden, SP=Spain, N= number of responses per country and overall,

***** significant at 1%, ** significant at 5%,** * significant at 10%,

All parameters were included as random parameters and assumed to be normally distributed. The estimation was conducted using 1000 Halton draws.

b) Contribution of each of the treatment attributes to the overall preference for a treatment choice
(mean per country, in percent (%) of total explained variance)

Country/N / Treatment Attribute	BE	NO	GE	SE	NL	UK	HU	SP	FR	IT	PT	RO	All *countries*
	33	41	44	24	63	40	71	63	40	59	39	42	559
Country Clusters	**Country Cluster 1**								**Country Cluster 2**				
Efficacy *Improvement DAS28*	44%	40%	42%	43%	44%	39%	46%	45%	43%	45%	39%	52%	44%
Safety *Probability of a serious AE*	10%	10%	9%	11%	1%	2%	12%	10%	20%	18%	19%	19%	12%
Patient´s Preference	14%	14%	14%	19%	17%	19%	16%	18%	21%	14%	14%	7%	16%
Cost-Effectiveness *ICER, QALY/year*	9%	12%	14%	10%	14%	21%	14%	10%	3%	8%	8%	4%	10%
Medication costs *per year, in local currency*	23%	24%	19%	17%	24%	19%	12%	17%	13%	15%	20%	18%	18%
Model fit, R^2	0.61	0.65	0.66	0.67	0.46	0.63	0.63	0.65	0.58	0.63	0.64	0.63	0.39

BE=Belgium, FR=France, GE=Germany, HU=Hungary, IT=Italy, NL=Netherlands, NO=Norway, PT=Portugal, RO=Romania, SE=Sweden, SP=Spain, N= number of responses per country and overall, DAS28= Disease Activity Score in 28 joints, AE=Adverse Event, ICER=Incremental Cost-Effectiveness Ratio, n.a.=not applicable, R^2=McFadden Pseudo R-squared

Table 3: Results latent class model distinguished 4 classes of respondents.

Latent class model (Responder type)	**Latent class 1** All attributes (except safety) balanced	**Latent class 2** Emphasis on efficacy, safety and patient´s preference, economic aspects less relevant,	**Latent class 3** All attributes except cost-effectiveness balanced	**Latent class 4** Emphasize on efficacy, patient dislike and costs
Average class probability [1)]	**43.2 %**	**22.6%**	**23.1 %**	**11.1 %**
Efficacy				
Moderate response	*Reference level*	*Reference level*	*Reference level*	*Reference level*
Good response	**1.98*** **	**3.65*** **	**2.32*** **	**1.74*** **
Remission	**3.08*** **	**6.39*** **	**3.38*** **	**3.85*** **
Safety				
Very rare	*Reference level*	*Reference level*	*Reference level*	*Reference level*
Rare	0.09	-**1.38***	**-0.96*** **	-0.44
Uncommon	-0.07	**-2.71*** **	**-2.45*** **	-0.58*
Patient´s preference				
favours treatment	**0.33*** **	**2.35*** **	**-0.37****	0.53
neutral	*Reference level*	*Reference level*	*Reference level*	*Reference level*
disfavours treatment	**-0.84*** **	**1.53*** **	**-1.34*** **	**-3.17*** **
Cost-effectiveness (10,000 EUR/QALY)	**-0.29*** **	-0.28*	-0.03	-0.07
Overall medication costs (1000 EUR/year)	**0.13****	-0.02	**-0.11*** **	**-0.09*** **
Constant	0.02	**-1.64*** **	**-0.22****	-0.34
Class probability model - cluster 2 [2)]	_____	**1.41*** **	**2.09*** **	1.16*

***** significant at 1%, ** significant at 5%,** * significant at 10%,

1) Average class probability = Probability that individual respondent chooses drug treatments according to respective responder types (all 559 responses from 12 countries included in the analysis)

2) Parameter estimates indicate that rheumatologists belonging to country cluster 2 (consisting of Romania, France, Portugal and Italy) compared to country cluster 1 (reference) are significantly more likely to be in classes 2, 3 or 4.

References

1. Pollard S, Bansback N, Bryan S. Physician attitudes toward shared decision making: A systematic review. Patient education and counseling. 2015 Sep; 98(9):1046-1057.
2. Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006 Nov; 10(42):iii-iv, xi-xiii, 1-229.
3. Jonsson B, Kobelt G, Smolen J. The burden of rheumatoid arthritis and access to treatment: uptake of new therapies. Eur J Health Econ. 2008 Jan; 8 Suppl 2:S61-86.
4. Putrik P, Ramiro S, Kvien TK, Sokka T, Uhlig T, Boonen A, et al. Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country's wealth? Annals of the rheumatic diseases. 2014 Nov; 73(11):2010-2021.
5. Stewart M, Brown JB, Donner A, McWhinney IR, Oates J, Weston WW, et al. The impact of patient-centered care on outcomes. J Fam Pract. 2000 Sep; 49(9):796-804.
6. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Annals of the rheumatic diseases. 2014 Mar; 73(3):492-509.
7. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Annals of the rheumatic diseases. 2010 Jun; 69(6):964-975.
8. Putrik P, Ramiro S, Kvien TK, Sokka T, Pavlova M, Uhlig T, et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. Annals of the rheumatic diseases. 2014 Jan; 73(1):198-206.
9. Jönssona B. RS, Wilking N. Cost effectiveness in practice and its effect on clinical outcomes. Journal of Cancer Policy. 2014; 2(1):10.
10. Richards M. Extent and causes of international variations in drug usage - A report for the Secretary of State for Health 2010.
11. Coast J, Al-Janabi H, Sutton EJ, Horrocks SA, Vosper AJ, Swancutt DR, et al. Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations. Health Econ. 2012 Jun; 21(6):730-741.
12. Ryan M. Discrete choice experiments in health care. Bmj. 2004 Feb 14; 328(7436):360-361.
13. van der Velde G, Pham B, Machado M, Ieraci L, Witteman W, Bombardier C, et al. Cost-effectiveness of biologic response modifiers compared to disease-modifying antirheumatic drugs for rheumatoid arthritis: a systematic review. Arthritis Care Res (Hoboken). 2011 Jan; 63(1):65-78.
14. Augustovski F, Beratarrechea A, Irazola V, Rubinstein F, Tesolin P, Gonzalez J, et al. Patient preferences for biologic agents in rheumatoid arthritis: a discrete-choice experiment. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2013 Mar-Apr; 16(2):385-393.
15. Muhlbacher AC, Nubling M. Analysis of physicians' perspectives versus patients' preferences: direct assessment and discrete choice experiments in the therapy of multiple myeloma. Eur J Health Econ. 2011 Jun; 12(3):193-203.
16. Muhlbacher AC, Lincke HJ, Nubling M. Evaluating patients' preferences for multiple myeloma therapy, a Discrete-Choice-Experiment. Psychosoc Med. 2008; 5:Doc10.
17. Barton JL. Patient preferences and satisfaction in the treatment of rheumatoid arthritis with biologic therapy. Patient Prefer Adherence. 2009; 3:335-344.

18. Tang B, Rahman M, Waters HC, Callegari P. Treatment persistence with adalimumab, etanercept, or infliximab in combination with methotrexate and the effects on health care costs in patients with rheumatoid arthritis. Clin Ther. 2008 Jul; 30(7):1375-1384.
19. Kievit W, Adang EM, Fransen J, Kuper HH, van de Laar MA, Jansen TL, et al. The effectiveness and medication costs of three anti-tumour necrosis factor alpha agents in the treatment of rheumatoid arthritis from prospective clinical practice data. Annals of the rheumatic diseases. 2008 Sep; 67(9):1229-1234.
20. Kievit W, van Hulst L, van Riel P, Fraenkel L. Factors that influence rheumatologists' decisions to escalate care in rheumatoid arthritis: results from a choice-based conjoint analysis. Arthritis Care Res (Hoboken). 2010 Jun; 62(6):842-847.
21. Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K, et al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. Health Technol Assess. 2011 Mar; 15(14):1-278.
22. Schoels M, Wong J, Scott DL, Zink A, Richards P, Landewe R, et al. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Annals of the rheumatic diseases. 2010 Jun; 69(6):995-1003.
23. Aletaha D, Landewe R, Karonitsch T, Bathon J, Boers M, Bombardier C, et al. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. Arthritis and rheumatism. 2008 Oct 15; 59(10):1371-1377.
24. de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics: a review of the literature. Health Econ. 2012 Feb; 21(2):145-172.
25. Ngene. [http://www.choice-metrics.com/].
26. Reed Johnson F, Lancsar E, Marshall D, Kilambi V, Muhlbacher A, Regier DA, et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2013 Jan-Feb; 16(1):3-13.
27. Currency converter. http://wwwxecom/currencyconverter/. last accessed March 2014.
28. https://www.limdep.com/products/nlogit/.
29. Hiligsmann M, Dellaert BG, Dirksen CD, van der Weijden T, Goemaere S, Reginster JY, et al. Patients' preferences for osteoporosis drug treatment: a discrete-choice experiment. Arthritis research & therapy. 2014; 16(1):R36.
30. NK Malhotra DB. Marketing research: An applied approach. Pearson Education. 2007.
31. StataCorp. 2011. Stata Statistical Software: Release 12. College Station TSL.
32. de Bekker-Grob EW, Rose JM, Donkers B, Essink-Bot ML, Bangma CH, Steyerberg EW. Men's preferences for prostate cancer screening: a discrete choice experiment. Br J Cancer. 2013 Feb 19; 108(3):533-541.
33. Oliver K, Innvar S, Lorenc T, Woodman J, Thomas J. A systematic review of barriers to and facilitators of the use of evidence by policymakers. BMC Health Serv Res. 2014; 14:2.
34. Joensuu JT, Huoponen S, Aaltonen KJ, Konttinen YT, Nordstrom D, Blom M. The cost-effectiveness of biologics for the treatment of rheumatoid arthritis: a systematic review. PLoS One. 2015; 10(3):e0119683.
35. Prosser LA, Koplan JP, Neumann PJ, Weinstein MC. Barriers to using cost-effectiveness analysis in managed care decision making. The American journal of managed care. 2000 Feb; 6(2):173-179.
36. Cleemput I, Neyt M, Thiry N, De Laet C, Leys M. Using threshold values for cost per quality-adjusted life-year gained in healthcare decisions. International journal of technology assessment in health care. 2011 Jan; 27(1):71-76.