

# A discrete choice experiment on preferences of patients with rheumatoid arthritis regarding disease-modifying antirheumatic drugs: the identification, refinement, and selection of attributes and levels

Elke GE Mathijssen<sup>1</sup>  
Milou van Heuckelum<sup>2</sup>  
Liset van Dijk<sup>3</sup>  
Marcia Vervloet<sup>3</sup>  
Simone MT Zonnenberg<sup>1</sup>  
Johanna E Vriezolk<sup>1</sup>  
Bart JF van den Bemt<sup>2</sup>

<sup>1</sup>Department of Rheumatology, Sint Maartenskliniek, Nijmegen, the Netherlands; <sup>2</sup>Department of Rheumatology and Pharmacy, Sint Maartenskliniek, Nijmegen, the Netherlands; <sup>3</sup>Netherlands Institute for Health Services Research (NIVEL), Utrecht, the Netherlands

Correspondence: Elke GE Mathijssen  
Department of Rheumatology, Sint  
Maartenskliniek, PO Box 9011,  
Nijmegen, the Netherlands  
Tel +31 24 365 9185  
Email e.mathijssen@maartenskliniek.nl

**Objective:** To comprehensively describe the identification, refinement, and selection of attributes and levels for a discrete choice experiment (DCE) on preferences of patients with rheumatoid arthritis (RA) regarding disease-modifying antirheumatic drugs (DMARDs).

**Methods:** A mixed-methods approach, consisting of three consecutive steps: a literature review, expert recommendations, and focus groups. Attributes and levels were identified by a scoping review and compiled into a list that was evaluated on its relevance by an expert panel. The list that resulted thereafter was used to inform three focus groups, including 23 patients with RA. New attributes and levels could be identified during the focus groups. Also, a ranking exercise was performed. The patients individually ranked the attributes (ie, the ones on the list and newly identified attributes) by relevance. The patients' individual rankings were summed to derive a ranking at group level and make an a priori selection of the most relevant attributes. The group discussions were transcribed for qualitative analysis.

**Results:** Nineteen attributes, each specified by two to seven levels, were identified by the scoping review. The expert recommendations resulted in the removal of one attribute. Furthermore, two new attributes and levels were identified and two attributes were split into two. One new attribute was identified during the focus groups. The results of the ranking exercise and qualitative analysis led to the refinement and selection of the following attributes: route of administration, frequency of administration, chance of efficacy, onset of action, risk of serious infections, risk of liver injury, and risk of cancer. Each attribute was specified by three levels.

**Conclusion:** This study contributes to the limited literature on the development of attributes and levels. Future research should pay more attention to a comprehensive description of this process. It ensures transparency and thereby allows researchers to judge a DCE's quality and generalizability.

**Keywords:** discrete choice experiment, mixed-methods, patient preferences, rheumatoid arthritis, disease-modifying antirheumatic drugs

## Introduction

Treatment of rheumatoid arthritis (RA) rests primarily on the long-term use of disease-modifying antirheumatic drugs (DMARDs). It is recommended to start DMARD therapy as soon as possible after the diagnosis is confirmed.<sup>1,2</sup> Early initiation enables optimal control of disease progression, reduces radiological damage and

improves patients' functioning and prognosis.<sup>3</sup> However, the full benefits of DMARDs are often not realized because many patients are non-adherent (ie, they do not take their medication as prescribed). Empirical studies showed adherence rates varying from 30% to 80%.<sup>4</sup> Non-adherence contributes to poor clinical outcomes and increased healthcare utilization and costs.<sup>5</sup> Patient preferences play an important role in adherence. Patients are more likely to be satisfied with and adhere to a treatment that is in line with their preferences.<sup>4,6</sup> Therefore, along with clinical guidelines, preferences of patients with RA should provide direction in making choices regarding DMARD therapy.<sup>1,2</sup>

Discrete choice experiments (DCEs) are increasingly used to elicit patient preferences.<sup>7</sup> They are based on the assumption that a treatment can be described by its characteristics, also referred to as attributes (eg, for medication: route of administration). Attributes in turn are specified by several levels (eg, for route of administration: oral, subcutaneous and intravenous). DCEs are typically implemented in surveys consisting of a series of choice tasks.<sup>8-11</sup> A choice task consists of two or more realistic, but hypothetical, treatments between which patients are asked to choose. Treatments are described by a number of attributes and each attribute takes one of several levels. Patients' choices provide information on the relative importance of the attributes and the trade-offs that they are willing to make between them. Furthermore, the exact influence of each level on their choices can be quantified through statistical modeling.<sup>12</sup>

In recent years, several studies have used a DCE to elicit preferences of patients with RA regarding DMARDs.<sup>13-16</sup> These studies reported extremely briefly on the development of attributes and levels. They only described the methods that were used to identify attributes and levels (eg, a literature review, interviews, and focus groups). Detailed information about search strings, eligibility criteria, interview guides and so forth were lacking. The development of attributes and levels is, however, a fundamentally important process. The validity of a DCE largely depends on the researchers' ability to specify relevant attributes and levels.<sup>8-10,17</sup> Due to the brevity of reporting in previous research, it is unclear whether the development of attributes and levels is conducted rigorously.<sup>18</sup> A comprehensive description of this process ensures transparency and thereby allows researchers to judge a DCE's quality and generalizability.<sup>18</sup> It also provides a reference point for future studies. Therefore, the aim of this study was to comprehensively describe the identification, refinement, and selection of attributes and levels for a DCE on preferences of patients with RA regarding DMARDs.

## Methods

A variety of methods are being used to develop attributes and levels for a DCE, including a literature review, expert recommendations, existing health outcome measures, surveys, interviews, and focus groups.<sup>17,18</sup> The use of qualitative methods, before, alongside or after other methods, is highly recommended by experts in the field.<sup>8-10,18,19</sup> Qualitative methods have the particular advantage of allowing researchers to draw on the views of future respondents. This minimizes the potential for misspecification of attributes and levels through overreliance on the researchers' own views.<sup>18</sup> In this study, a mixed-method approach was used. It consisted of three consecutive steps: 1) a literature review; 2) expert recommendations; and 3) focus groups.

### Step I: A literature review

A scoping review was performed to rapidly examine the extent, range and nature of research activity.<sup>20</sup> The framework of Arksey and O'Malley<sup>20</sup> was followed. This framework provides a comprehensive foundation for scoping review methodology and comprises five stages: 1) identifying the research question; 2) identifying relevant studies; 3) study selection; 4) charting the data; and 5) collating, summarizing and reporting the results.<sup>20</sup>

#### Identifying the research question

The following research question was identified: What attributes and levels of DMARDs, used to treat RA, can be identified from the literature?

#### Identifying relevant studies

The databases of PubMed, Embase and CINAHL were searched from inception to October 2016, using both Medical Subject Headings (MeSH) terms and free text words. There were no restrictions on study designs. Only publications written in English were included. Table 1 shows the search strings that were used.

#### Study selection

After combining the search results from the three databases, duplicates were removed. The remaining publications were screened for inclusion on two levels. The first level concerned a screening on title and abstract and the second level a screening of the full texts. The inclusion criteria were: 1) studies on adult (ie, aged 18 years or older) patients with RA; and 2) studies on attributes of DMARDs, preferences for DMARDs or experiences with DMARDs. Two researchers (EM and MV) independently screened the publications on title and abstract. The full texts of the publications that met the inclusion criteria were obtained and independently screened by the same researchers. The publications were excluded if they did not meet the inclusion criteria.

**Table 1** Search strings

PubMed	CINAHL	Embase
(Rheumatoid arthritis [MeSH] OR Rheumatoid arthritis)	(MH "Arthritis, Rheumatoid+" OR Rheumatoid arthritis)	exp Rheumatoid arthritis/ OR Rheumatoid arthritis.mp.
AND	AND	AND
(Antirheumatic agents [MeSH] OR Antirheumatic agents OR DMARDs OR DMARD OR Azathioprine OR Methotrexate OR Sulfasalazine OR Hydroxychloroquine OR Auranofin OR Leflunomide OR Etanercept OR Adalimumab OR Golimumab OR Infliximab OR Certolizumab OR Abatacept OR Tocilizumab OR Rituximab)	(MH "Antirheumatic Agents+" OR antirheumatic agents OR DMARDs OR DMARD OR Azathioprine OR Methotrexate OR Sulfasalazine OR Hydroxychloroquine OR Auranofin OR Leflunomide OR Etanercept OR Adalimumab OR Golimumab OR Infliximab OR Certolizumab OR Abatacept OR Tocilizumab OR Rituximab)	exp Antirheumatic agent/ OR Antirheumatic agents.mp. OR DMARDs.mp. OR DMARD.mp. OR Methotrexate.mp. OR Azathioprine.mp. OR Sulfasalazine.mp. OR Hydroxychloroquine.mp. OR Auranofin.mp. OR Leflunomide.mp. OR Etanercept.mp. OR Adalimumab.mp. OR Golimumab.mp. OR Infliximab.mp. OR Certolizumab.mp. OR Abatacept.mp. OR Tocilizumab.mp. OR Rituximab.mp.
AND	AND	AND
(preferences OR attributes OR experiences)	(preferences OR attributes OR experiences)	preferences.mp. OR attributes.mp. OR experiences.mp.

**Abbreviations:** DMARD, disease-modifying antirheumatic drug; MeSH, Medical Subject Headings.

In case of disagreement a third researcher (LvD) was decisive in including or excluding the publications.

### Charting the data and collating, summarizing and reporting the results

For each of the included publications data were charted: author(s) (year of publication), objective(s), study design, study population and sample size, attributes (levels), and conclusion. This was done by three researchers (EM, MV and MvH). Each researcher charted a part of the data. Based on the data chart, attributes and levels were identified and the researchers jointly compiled a list.

### Step 2: Expert recommendations

The list of attributes and levels was evaluated by an expert panel. A purposive sampling approach was used to recruit two rheumatologists, two pharmacists, two rheumatology nurses or nurse practitioners, two researchers, and two patients with RA. The experts were not in any other way involved in this study. The list was sent to them by email and provided with a brief instruction. The experts were instructed to independently comment on the relevance of the attributes and levels. Also, they were encouraged to add new attributes and levels to the list. Their recommendations were processed by the researchers. This resulted in a more comprehensive list that was used to inform the focus groups.

### Step 3: Focus groups

#### Patient recruitment

Patients were recruited from the outpatient pharmacy of the Sint Maartenskliniek in Nijmegen, the Netherlands and the

local rheumatology patient association in 's-Hertogenbosch, the Netherlands. A convenience sampling approach was used. Eligibility criteria were: 1) a diagnosis of RA, confirmed by a rheumatologist; 2) aged 18 years or older; and 3) proficiency in the Dutch language. An invitation letter and informed consent form were sent to eligible patients. Personal experiences of the researchers with this recruitment technique (ie, impersonal invitations for focus groups on predetermined dates and times) showed response rates of 5%–10%. Therefore, a group of 400 patients was invited.

#### Data collection

The focus groups were facilitated by an independent, experienced moderator (AH) and an assistant moderator (EM). A discussion guide, including engagement, exploratory and exit questions, was used to standardize and structure the data collection (Figure S1).<sup>21</sup> All focus groups were audio recorded and subsequently transcribed verbatim by a professional transcription service. Before the start of the focus groups, each patient completed a brief questionnaire on socio-demographic and clinical characteristics, including age, gender, educational level, employment status, disease duration, and current DMARD use.

The focus groups were divided into two parts. First, the patients individually wrote down attributes and levels of DMARDs that were important to them in making choices regarding DMARD therapy. This was followed by a group discussion. Second, a ranking exercise was performed to scale down the number of attributes to a number manageable within a DCE. There is no consensus in the literature on what counts as a manageable number. Reviews showed that, in practice, most DCEs included a number of attributes between

four and seven.<sup>11,22</sup> The list of attributes and levels derived from the literature review and expert recommendations was presented to the patients. They were asked to individually rank the attributes by relevance. Rank one represented the most relevant attribute. Attributes that were newly identified during the first part of the focus group could also be ranked. A group discussion on the patients' individual rankings and the wording of the attributes and levels was held afterwards.

### Data analysis

The patients' individual rankings were summed to derive a ranking at group level and make an a priori selection of the most relevant attributes. The transcripts were analyzed using a thematic analysis method.<sup>23</sup> This was done independently by two researchers (MvH and SZ). Both a deductive and inductive approach were used. The codes and themes were pre-selected based on the list of attributes and levels. The inductive approach led to a revision of the pre-selected codes and themes. Additionally, new ones were identified. The inductive approach also made it possible for the researchers to gain a deeper insight into the relevance of the attributes and levels from the view of patients with RA. The software program MAXQDA 10 was used for the qualitative analysis. It was checked whether data saturation occurred. This was defined as the point where no new codes and themes were identified.<sup>24</sup> Also, a member check was performed. A summary of the discussions was sent to the patients by email and they were asked to comment on its accuracy. Eventually, the results of the ranking exercise and qualitative analysis were extensively discussed by the researchers and decisions on the selection of attributes and levels in the DCE were jointly made. Two rheumatologists, who were not involved in the expert panel, were consulted for recommendations regarding the range of the levels.

### Pilot test

A series of choice tasks for the DCE were composed, using the selected attributes and levels. The choice tasks were implemented in a survey. Eleven patients with RA were invited to complete the survey. They were members of a local panel for patient participation in research. An invitation was sent to them by email and included a link to the survey. Also, a corresponding, open-ended questionnaire was attached (Box S1). Their understanding of the attributes and levels was reviewed. They were also asked to comment on the wording of the attributes and levels. Next to that, the pilot test reviewed the acceptability of the number of attributes and levels and total length of the survey.

## Ethical considerations

The medical research ethical committee (MREC) of Arnhem-Nijmegen, the Netherlands, waived ethical approval since the study was not subject to the medical research involving human subjects act (file number: 2016–2474). All patients signed informed consent for participation in the focus groups. Patient data were handled according to the applicable laws and regulations. Personal identifying information was replaced by study codes. A document that linked the study codes to the patients' identifying information was digitally stored and protected.

## Results

This study's mixed-methods approach consisted of three consecutive steps. In order to portray the whole process, the results are described step by step.

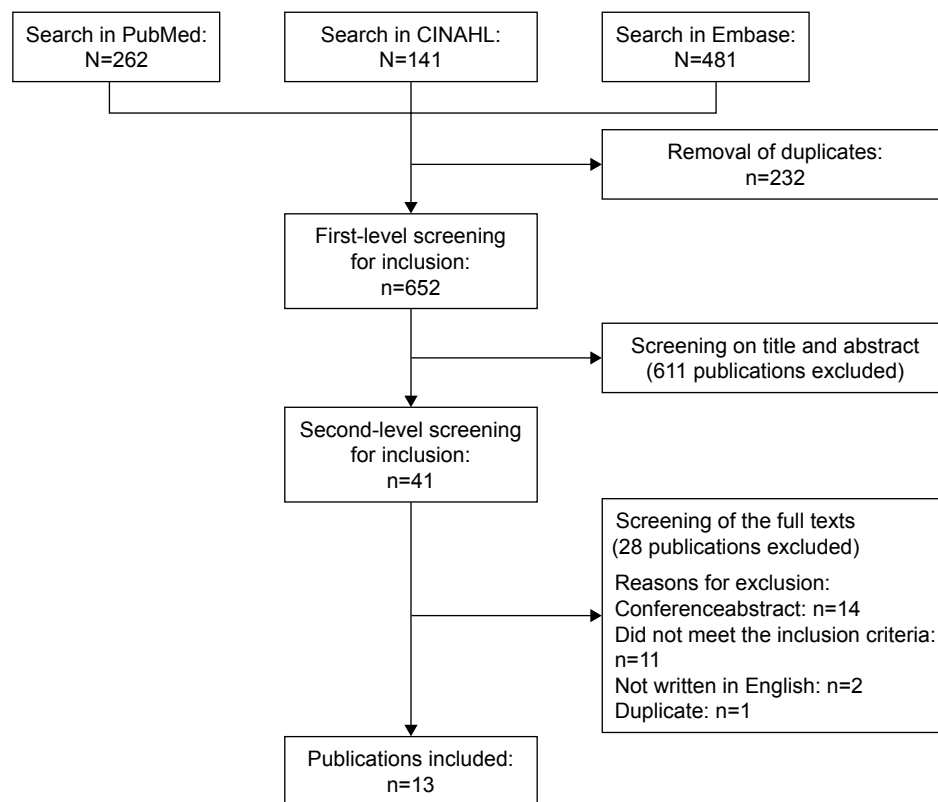
### Step 1: A literature review

The search generated 884 publications (PubMed: n=262; Embase: n=481; and CINAHL: n=141). After removing duplicates (n=232), 652 publications remained. The first-level screening on title and abstract led to the exclusion of 611 publications. Twenty-eight more publications were excluded after the second-level screening of the full texts: 14 publications were conference abstracts, 11 publications did not meet the inclusion criteria, two publications were not written in English and one publication turned out to be a previously overlooked duplicate. In total, 13 publications, representing 13 unique studies, were included.<sup>13–15,25–34</sup> Figure 1 shows the flowchart of the selection process.

Data were charted for each of the included publications (Table S1). Based on the data chart, 19 attributes were identified. Each attribute was specified by two to seven levels. Table 2 shows the list of attributes and levels that resulted after the literature review.

### Step 2: Expert recommendations

The evaluation of the experts resulted in the removal of one attribute (improvement in daily functioning). This attribute was specified by the levels "45% of the patients feel much better", "60% of the patients feel much better", and "75% of the patients feel much better". It was considered not specific enough and therefore likely to give rise to ambiguities. Two new attributes were identified: "required storage conditions" and "chance of injection side reaction". Regarding the attribute "frequency of administration" one new level (once every 12 weeks) was identified. One new level (at the general practice) was also identified regarding the attribute "location



**Figure 1** Flowchart selection process.

of administration”. Furthermore, the scope of two attributes “experience with DMARD” and “risk of dizziness, nausea, vomiting or diarrhea” was considered too broad. These attributes were split into two. The first was split into “years of experience with DMARD to treat RA” and “knowledge about long-term consequences of DMARD use” and the second was split into “risk of headache or dizziness” and “risk of gastrointestinal complications”. The result after the expert recommendations was a more comprehensive list of 22 attributes, each specified by two to eight levels.

### Step 3: Focus groups

Three focus groups including 23 patients with RA were conducted. The focus groups lasted between 90 and 120 minutes. Table 3 shows the socio-demographic and clinical characteristics of the patients.

#### Identification

The patients in the first and second focus group did not identify new attributes and levels. One new attribute (contraindicated during pregnancy and breast feeding) was identified during the third focus group. This attribute was also ranked. The highest ranked, and thus most relevant attributes at group level, were: 1) risk of cancer; 2) risk of liver injury;

3) chance of efficacy; 4) risk of joint damage; 5) onset of action; 6) risk of serious infections; and 7) knowledge about long-term consequences of DMARD use. “Costs” was the lowest ranked attribute. Table S2 includes the patients’ ranking. The group discussions mainly focused on the relevance of the attributes “route of administration” and “frequency of administration”. Also, the patients expressed their preferences for DMARDs with a low risk of side effects. Adjustments to the wording of the attributes and levels were not deemed necessary.

#### Refinement and selection

Based on the literature, the researchers decided to include seven attributes in the DCE.<sup>11,22</sup> The refinement and selection of the attributes and levels required some difficult decisions. The attributes “route of administration” and “frequency of administration” were not highly ranked. The results of the qualitative analysis, however, revealed that these attributes were relevant from the view of patients with RA. Indeed, the group discussions mainly focused on their relevance. It was therefore decided to include them anyway. The attributes “risk of joint damage” and “knowledge about long-term consequences of DMARD use” were highly ranked. Yet, it was decided not to include these attributes. The first was



**Table 2** List with attributes and levels

Attribute	Levels
Combination therapy	Yes No
Route of administration	Oral Subcutaneous Intravenous
Location of administration	At home At the hospital
Preparation of DMARD needed	Yes No
Frequency of administration	Daily Twice a day Weekly Every 2 weeks Every 4 weeks Every 8 weeks Every 6 months
Time needed for infusion	30 minutes 60 minutes 120 minutes 240 minutes
Experience with DMARD	More than 20 years of experience New DMARD with unknown long-term consequences
Chance of efficacy	40% 60% 75%
Onset of action	1 week 2 weeks 4 weeks 6 weeks 8 weeks
Improvement in daily functioning	45% of the patients feel much better 60% of the patients feel much better 75% of the patients feel much better
Risk of joint damage	60% of the patients develops no joint damage within 1 year 75% of the patients develops no joint damage within 1 year
Risk of cancer	No increased risk 0.1% increased risk
Risk of serious infections	1% increased risk 5% increased risk
Risk of liver injury	No increased risk 0.1% increased risk 1% increased risk
Risk of hair loss	No increased risk 10% increased risk
Risk of dizziness, nausea, vomiting or diarrhea	No increased risk 10% increased risk 30% increased risk
Risk of mouth ulcers	No increased risk 10% increased risk
Risk of skin rash	No increased risk 10% increased risk 40% increased risk

(Continued)

**Table 2** (Continued)

Attribute	Levels
Costs	500–1,000 euros per patient per year 1,000–10,000 euros per patient per year 10,000–15,000 euros per patient per year

**Abbreviation:** DMARD, disease-modifying antirheumatic drug.

considered to be dependent on the attribute “chance of efficacy”. The second was considered not specific enough since it was unclear how many years were meant by long-term. The researchers acted upon the consulted rheumatologists’ recommendations to include realistic levels. On the one hand, the range of levels had to be wide enough to induce trading behavior. On the other hand, however, levels had to be realistic in order to obtain clinically meaningful results.<sup>7</sup>

The results of the ranking exercise and qualitative analysis led to the refinement and selection of the following attributes: 1) route of administration; 2) frequency of administration; 3) chance of efficacy; 4) onset of action; 5) risk of serious infections; 6) risk of liver injury; and 7) risk of cancer. Each attribute was specified by three levels. Table 4 shows the attributes and levels that were eventually included in the DCE. Quotes from the transcripts of the focus groups were included in Table 4 to prove that decisions on the inclusion of attributes and levels were rooted in the patients’ voices.

## Pilot test

The survey and corresponding questionnaire were completed by five patients with RA. They had no difficulties in understanding the attributes and levels. The wording of the attributes and levels was also considered appropriate. The patients only noticed some minor typos that were corrected by the researchers. The pilot test revealed that both the number of attributes and total length of the survey were acceptable. All patients completed the survey in 15 to 20 minutes. Apart from the correction of typos, no adjustments were made to the attributes and levels.

## Discussion

In contrast to previous studies, this study comprehensively described the identification, refinement, and selection of attributes and levels for a DCE on preferences of patients with RA regarding DMARDs. The attributes and levels were developed using a mixed-method approach, consisting of three consecutive steps. A list of attributes and levels

**Table 3** Socio-demographic and clinical characteristics of the patients

Characteristic	Group 1 (N=8)	Group 2 (N=11)	Group 3 (N=4)	Total (N=23)
Age in years (median (range))	57 (52–78)	62 (38–78)	62.5 (36–68)	62 (36–78)
Gender (%)				
Male	0	18	25	13
Female	100	82	75	87
Educational level <sup>a</sup> (%)				
Low	38	73	0	48
Medium	25	27	50	30
High	38	0	50	22
Employment status (%)				
Employed	50	18	0	26
Unemployed	50	82	100	74
Disease duration in years (median (range))	7 (2–25)	8 (2–42)	16 (12–22)	11 (2–42)
Current DMARD use (%)				
sDMARD, methotrexate	50	27	75	44
sDMARD, other <sup>b</sup>	38	36	0	30
bDMARD, anti-TNF	50	46	50	48
bDMARD, other <sup>c</sup>	13	18	25	17

**Notes:** <sup>a</sup>Level of education: low = up to and including lower technical and vocational training; medium = up to and including secondary technical and vocational training; high = up to and including higher vocational training and university. <sup>b</sup>sDMARD, other: Hydroxychloroquine and Sulfasalazine. <sup>c</sup>bDMARD, other: Rituximab and Tocilizumab.

**Abbreviations:** DMARD, disease-modifying antirheumatic drug; TNF, tumor necrosis factor.

was derived from the first two steps (ie, a literature review and expert recommendations) and used to inform the focus groups in the third step. Eventually, these steps resulted in the selection of seven attributes, each specified by three levels.

A pilot test confirmed the appropriateness of the attributes and levels for inclusion in the DCE.

The following attributes were included: 1) route of administration; 2) frequency of administration; 3) chance

**Table 4** Included attributes and levels

Attribute	Levels	Quotes
Route of administration	Oral	• “I’d rather have pills than injections.” (Patient 103, female, 55 years)
	Subcutaneous	• “They did offer to put me on the drip once, but I do not want that. I want to be in control myself. [...] If I do the injections myself I still have the idea of being in control.” (Patient 203, female, 52 years)
	Intravenous	
Frequency of administration	Daily	• “I would not want to be on the drip too often, as it takes up a lot of time.” (Patient 301, female, 36 years)
	Weekly	• “[...] and then you have to take all those stupid pills in between. They determine your day. I cannot really cope with that.” (Patient 202, female, 45 years)
	Monthly	• “Taking something on a daily basis would not be acceptable to me. Then you’re always busy with your medicines.” (Patient 207, female, 67 years)
Chance of efficacy	40%	• “Well, I think it is important that the medicine works for me. That’s the main thing.” (Patient 205, male, 60 years)
	60%	• “It should work. I do not want to be ill. Period.” (Patient 106, female, 62 years)
	80%	• “How long it takes for the medicine to work. As soon as possible, as far as I’m concerned.” (Patient 108, female, 73 years)
Onset of action	1 week	
	6 weeks	
	12 weeks	
Risk of serious infections	No increased risk	• “I have used a biological for 3 months. But it didn’t work for me so I was allowed to stop using it. I was so frightened when I read about things like infections. Then I thought: oh no! Actually ... I was happy when I could stop using it.” (Patient 303, female, 62 years)
	0.5% increased risk	
	1% increased risk	
Risk of liver injury	No increased risk	• “To me, my health is my greatest wealth. [...], the risk of kidney or liver injury. [...] These are things that matter to me.” (Patient 203, female, 52 years)
	0.1% increased risk	
	1% increased risk	
Risk of cancer	No increased risk	• “What else do I find important? The risk of cancer. [...] I am very frightened of that, cancer.” (Patient 211, female, 78 years)
	0.1% increased risk	
	0.5% increased risk	

of efficacy; 4) onset of action; 5) risk of serious infections; 6) risk of liver injury; and 7) risk of cancer. The attributes “route of administration” and “frequency of administration” were also included in all previous studies.<sup>13–16</sup> This study confirmed that these attributes are highly relevant when considering attributes for inclusion in comparable DCEs. During the focus groups, preferences for DMARDs with a low risk of side effects were expressed by the patients. Comparable DCEs should therefore be considered to include attributes referring to side effects. Side effects differ in severity. It is important to realize that severity is a subjective term. What is severe to one person may not necessarily be severe to another. In order to avoid ambiguous interpretations one should not use such subjective terms (eg, risk of severe side effects). Whereas one previous study also included the attribute “costs”,<sup>13</sup> this study showed its irrelevance for inclusion in the DCE. This may be explained by the fact that, in the Netherlands, DMARD therapy is covered by health insurance. There are no out-of-pocket costs involved for patients. Obviously, this attribute is context-specific and not easily generalizable.

It is clear that the included attributes are important to patients with RA in making choices regarding DMARD therapy. Research has shown that there is an association between a decision making process in which healthcare providers take account of what is important to patients and higher treatment satisfaction.<sup>4,6</sup> Treatment satisfaction in turn is associated with improved adherence.<sup>35</sup> Patients are more likely to adhere to a treatment they are satisfied with. In clinical practice, it is therefore worthwhile paying attention to the included attributes when aiming to improve adherence. Healthcare providers should take them into account in the decision making process. The DCE will eventually provide insight into the relative importance of the included attributes.

This study’s mixed-methods approach has been found highly suitable to identify, refine and select attributes and levels for a DCE. The benefits of several methods (ie, a literature review, expert recommendations, and focus groups) were utilized. A list of attributes and levels was derived from the literature review and expert recommendations. These two steps allowed a quick identification of attributes and levels. The list also proved to be comprehensive since only one new attribute was identified by the patients in the third focus group. It can therefore be argued that meanwhile there is sufficient literature available to identify attributes and levels of DMARDs, used to treat RA.

It is, however, crucial to use qualitative methods for the refinement and selection of attributes and levels.

Qualitative analysis made it possible for the researchers to gain a deeper insight into the relevance of the attributes and levels from the view of patients with RA. Thus, the potential for misspecification through overreliance on the researchers’ own views was minimized. In this study, decisions on the inclusion of attributes and levels were rooted in the patients’ voices (Table 4). Moreover, attributes and levels should be clearly described and explained where needed since they are frequently misunderstood.<sup>18</sup> During the focus groups, the patients commented on the wording of the attributes and levels. This resulted in the inclusion of attributes and levels that are understandable to the DCE’s target group.

One of the challenges of selecting attributes and levels for inclusion is related to scaling down the often large number of attributes to a number manageable within a DCE. Although there is no fixed threshold number, the number of attributes is usually limited to ten.<sup>11,22</sup> Beyond that, the choice tasks will get too complex. Hiligsmann et al used a nominal group technique to identify the most relevant attributes for inclusion.<sup>36</sup> They suggested that the use of a simple ranking exercise, such as the one in this study, may also be sufficient for this purpose. Abiiro et al also suggested to use simple quantitative tools for this purpose.<sup>37</sup> However, they stated that qualitative reasoning would still be required to guarantee relevant attributes and levels. Their statement was supported by this study. The attribute “frequency of administration”, for example, was not highly ranked. Nevertheless, it was included anyway based on the results of the qualitative analysis.

Several strengths and limitations of this study deserve attention. A strength was its mixed-methods approach. The methods that were used in this study have different pros and cons and complemented each other. The analysis of the qualitative data (ie, transcripts) was another strength. Researchers triangulation led to a broader and deeper understanding of the data. Moreover, bias was limited because of incorporating control on each other’s interpretations. The literature search was limited to the databases of PubMed, Embase and CINAHL. Relevant studies indexed only in other databases (eg, PsycINFO) may have been missed. However, this study has shown that the vast majority of attributes and levels were identified by the scoping review. It is unlikely that other studies, although relevant, would have resulted in the identification of new attributes and levels. Additionally, DMARDs not licensed in Europe at the time of the literature search, such as tofacitinib, were not included as search terms. This has not affected the validity of the results since studies investigating these DMARDs were still



found by other search terms. These DMARDs also do not have attributes and levels that differ from the ones that were identified in this study. When using qualitative methods, Coast et al recommended an iterative process between data collection and analysis.<sup>18</sup> In this study, the data were collected in advance and then analyzed. This was a limitation. However, it was checked whether data saturation occurred. If this had not been the case, additional focus groups would have been conducted. Another limitation is the convenience sampling approach that was used to recruit patients for the focus groups. According to Coast et al, the potential for misspecification of attributes and levels always exists, even when qualitative methods are used.<sup>18</sup> It is therefore recommended to use a purposive sampling approach in order to obtain a full range of views. Nevertheless, the patients in this study turned out to represent a mix of socio-demographic and clinical characteristics.

## Conclusion

In this study, recently recommended methods to identify, refine, and select attributes and levels for a DCE were used and comprehensively described. Moreover, the suitability of a mixed-methods approach was highlighted. This study contributes to the limited literature on the development of attributes and levels for a DCE. Future research should pay more attention to a comprehensive description of this process. This ensures transparency and thereby allows researchers to judge a DCE's quality and generalizability.

## Acknowledgments

The authors would like to acknowledge Annette Heinen for facilitating the focus groups as a moderator and Peter van Grinsven and Manorma Dwarkasing for participating as patient representatives in this study.

This study was supported by funding from Pfizer Incorporated. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Singh JA, Saag KG, Bridges SL Jr, et al. American college of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2015;2016(68):1–26.
- Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017;76(6):960–977.
- Emery P. Evidence supporting the benefit of early intervention in rheumatoid arthritis. *J Rheumatol Suppl*. 2002;66:3–8.
- van den Bemt BJ, Zwikker HE, van den Ende CH. Medication adherence in patients with rheumatoid arthritis: a critical appraisal of the existing literature. *Expert Rev Clin Immunol*. 2012;8(4):337–351.
- Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487–497.
- Barton JL. Patient preferences and satisfaction in the treatment of rheumatoid arthritis with biologic therapy. *Patient Prefer Adherence*. 2009;3:335–344.
- Mühlbacher A, Johnson FR. Choice experiments to quantify preferences for health and healthcare: state of the practice. *Appl Health Econ Health Policy*. 2016;14(3):253–266.
- Louviere J, Swait J, Hensher D. *Stated Choice Methods: Analysis and Application*. 1st ed. Cambridge: Cambridge University Press; 2000.
- Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. *Pharmacoeconomics*. 2008;26(8):661–677.
- Louviere JJ, Lancsar E. Choice experiments in health: the good, the bad, the ugly and toward a brighter future. *Health Econ Policy Law*. 2009;4(Pt 4):527–546.
- de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics: a review of the literature. *Health Econ*. 2012;21(2):145–172.
- Hauber AB, González JM, Groothuis-Oudshoorn CG, et al. Statistical methods for the analysis of discrete choice experiments: a report of the ISPOR Conjoint Analysis Good Research Practices Task Force. *Value Health*. 2016;19(4):300–315.
- Augustovski F, Beratarrechea A, Irazola V, et al. Patient preferences for biologic agents in rheumatoid arthritis: a discrete-choice experiment. *Value Health*. 2013;16(2):385–393.
- Poulos C, Hauber AB, González JM, Turpcu A. Patients' willingness to trade off between the duration and frequency of rheumatoid arthritis treatments. *Arthritis Care Res*. 2014;66(7):1008–1015.
- Hazlewood GS, Bombardier C, Tomlinson G, et al. Treatment preferences of patients with early rheumatoid arthritis: a discrete-choice experiment. *Rheumatology*. 2016;55(11):1959–1968.
- Alten R, Krüger K, Rellecke J, et al. Examining patient preferences in the treatment of rheumatoid arthritis using a discrete-choice approach. *Patient Prefer Adherence*. 2016;10:2217–2228.
- Mangham LJ, Hanson K, Mcpake B, do Hto. How to do (or not to do) ... Designing a discrete choice experiment for application in a low-income country. *Health Policy Plan*. 2009;24(2):151–158.
- Coast J, Al-Janabi H, Sutton EJ, et al. Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations. *Health Econ*. 2012;21(6):730–741.
- Bridges JF, Hauber AB, Marshall D, et al. Conjoint analysis applications in health – a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. *Value Health*. 2011;14(4):403–413.
- Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol*. 2005;8(1):19–32.
- Krueger RA. *Developing Questions For Focus Groups*. 1st ed. Thousand Oaks: CA: Sage publications; 1998.
- Marshall D, Bridges JF, Hauber B, et al. Conjoint analysis applications in health – how are studies being designed and reported?: an update on current practice in the published literature between 2005 and 2008. *Patient*. 2010;3(4):249–256.
- Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol*. 2006;3(2):77–101.
- Creswell JW. *Qualitative Research Design: Quantitative and Mixed Methods Approaches*. 3rd ed. Thousand Oaks, CA: Sage Publications; 2009.
- Fraenkel L, Bogardus ST, Concato J, Felson DT, Wittink DR. Patient preferences for treatment of rheumatoid arthritis. *Ann Rheum Dis*. 2004;63(11):1372–1378.
- Chilton F, Collett RA. Treatment choices, preferences and decision-making by patients with rheumatoid arthritis. *Musculoskeletal Care*. 2008;6(1):1–14.

27. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Patient preferences for treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial). *Ann Rheum Dis*. 2007;66(9):1227–1232.
28. Lisicki R, Chu L. What matters to patients and physicians when considering biologic therapy for rheumatoid arthritis. *Postgrad Med*. 2008;120(3):154–160.
29. Constantinescu F, Goucher S, Weinstein A, Smith W, Fraenkel L. Understanding why rheumatoid arthritis patient treatment preferences differ by race. *Arthritis Rheum*. 2009;61(4):413–418.
30. Scarpato S, Antivalle M, Favalli EG, et al. Patient preferences in the choice of anti-TNF therapies in rheumatoid arthritis. Results from a questionnaire survey (RIVIERA study). *Rheumatology*. 2010;49(2): 289–294.
31. Huynh TK, Ostergaard A, Egsmose C, Madsen OR. Preferences of patients and health professionals for route and frequency of administration of biologic agents in the treatment of rheumatoid arthritis. *Patient Prefer Adherence*. 2014;8:93–99.
32. Bolge SC, Goren A, Brown D, Ginsberg S, Allen I. Openness to and preference for attributes of biologic therapy prior to initiation among patients with rheumatoid arthritis: patient and rheumatologist perspectives and implications for decision making. *Patient Prefer Adherence*. 2016;10:1079–1090.
33. Louder AM, Singh A, Saverno K, et al. Patient preferences regarding rheumatoid arthritis therapies: a conjoint analysis. *Am Health Drug Benefits*. 2016;9(2):84–93.
34. Nolla JM, Rodríguez M, Martín-Mola E, et al. Patients' and rheumatologists' preferences for the attributes of biological agents used in the treatment of rheumatic diseases in Spain. *Patient Prefer Adherence*. 2016;10: 1101–1113.
35. Barbosa CD, Balp MM, Kulich K, Germain N, Rofail D. A literature review to explore the link between treatment satisfaction and adherence, compliance, and persistence. *Patient Prefer Adherence*. 2012; 6:39–48.
36. Hiligsmann M, van Durme C, Geusens P, et al. Nominal group technique to select attributes for discrete choice experiments: an example for drug treatment choice in osteoporosis. *Patient Prefer Adherence*. 2013; 7:133–139.
37. Abihiro GA, Leppert G, Mbera GB, Robyn PJ, de Allegri M. Developing attributes and attribute-levels for a discrete choice experiment on micro health insurance in rural Malawi. *BMC Health Serv Res*. 2014; 14:235.

## Supplementary materials

<b>Engagement questions</b>	<p>1) Could you tell us something about yourself? For example, what DMARD(s) do you currently use?</p> <p>This question was asked to the patients in a round robin fashion.</p>
<b>Exploratory questions</b>	<p><b>Part 1</b></p> <p>The definition of attributes and levels (ie, what are attributes and levels?) was explained to the patients.</p> <p>2) What attributes and levels are important to you in making choices regarding DMARD therapy? Write down what comes to your mind.</p> <p>The patients could individually write down their answers on a blank paper.</p> <p>3) What did you write down?</p> <p>This question was asked to the patients in a round robin fashion. All answers were written on a flip chart by the assistant moderator.</p> <p>4) What attributes and levels are most important to you? Pick three from the flip chart and explain your choices.</p> <p>This question was asked to the patients in a round robin fashion. The patients' choices were tallied on the flip chart.</p> <p>5) Take a look at the flip chart. Have you missed anything?</p> <p><b>Part 2</b></p> <p>The list with conceptual attributes and levels derived from the literature review and expert recommendations was presented to the patients.</p> <p>6) Could you rank the attributes by importance?</p> <p>The patients could individually rank the attributes on a work sheet. Newly identified attributes could also be ranked.</p> <p>7) What are your highest ranked attributes (please explain your answer)?</p> <p>8) What are your lowest ranked attributes (please explain your answer)?</p> <p>9) What do you think about the wording of the attributes and levels?</p>
<b>Exit questions</b>	<p>10) Is there anything else you would like to share with us?</p>

**Figure S1** Discussion guide.

**Abbreviation:** DMARD, disease-modifying antirheumatic drug.

- How long did it take you to complete the survey?
- What do you think about the length of the survey?
- How difficult was it for you to complete the survey?
- Are the questions in the survey well explained (please explain your answer)?
- Have you missed anything in the survey?
- Do you have any suggestions about how to improve the survey?

**Box S1** Open-ended questionnaire.

Table S1 Data chart

Publication	Objective(s)	Study design	Study population and sample size	Attributes (levels)	Conclusion
Augustovski et al <sup>13</sup>	<ul style="list-style-type: none"> <li>Identify the extent to which the attributes of a treatment (eg, efficacy, mode of administration, adverse events and costs) affect patients' choice of treatment.</li> <li>Determine the hierarchical importance of these attributes.</li> </ul>	Discrete choice experiment (DCE)	<ul style="list-style-type: none"> <li>Inclusion criteria for study participants were: 1) age greater than 18 years; 2) diagnosis of rheumatoid arthritis (RA) according to the American College of Rheumatology (ACR) of more than 6 months; 3) treatment by a rheumatologist in an ambulatory setting; 4) taking at least a disease-modifying antirheumatic drug (DMARD); and 5) being naive to biologic agents (BAs).</li> <li>Sample size: 240 patients.</li> </ul>	<ul style="list-style-type: none"> <li>Mode of administration (oral, subcutaneous, intravenous)</li> <li>Frequency of administration (every 10 months, every month, every week, every day)</li> <li>Local adverse events (no risk, 15 patients out of 100, 40 patients out of 100)</li> <li>Generalized adverse events (no risk, 15 patients out of 100, 40 patients out of 100)</li> <li>Serious infections (1 patient out of 100, 5 patients out of 100)</li> <li>Costs (no out-of-pocket costs, \$500 per month, \$1,500 per month)</li> </ul>	<p>Different treatment attributes had a significant and different influence in RA patients' choice of BAs. This type of study cannot only inform about patients' preferences but also about the trade-offs among different possible treatments or process-related attributes.</p>
Bolge et al <sup>22</sup>	<ul style="list-style-type: none"> <li>To examine openness to and preference for attributes of biologic therapies among patients with RA prior to biologic therapy initiation.</li> <li>To examine rheumatologist perceptions of patient openness to and preference among biologic therapies.</li> <li>To identify gaps between rheumatologist and patient perceptions about biologic therapies and corresponding discussions about biologic therapies, as well as implications for patient-rheumatologist dialog and the decision making process surrounding biologic therapy treatment for RA.</li> </ul>	Online survey	<ul style="list-style-type: none"> <li>Patient inclusion criteria: 1) self-reported diagnosis of RA by a rheumatologist; 2) visited a rheumatologist for RA in the past 6 months; 3) currently taking DMARDs; 4) never taken a biologic therapy; 5) aware of and discussed biologic therapy with rheumatologist; 6) aged 18 years or older; 7) residing in the US; 8) able to read/write English; and 9) provided online informed consent.</li> <li>Rheumatologist inclusion criteria: 1) specialty in rheumatology, board certified or eligible; 2) 2–25 years post residency practice as a rheumatologist; 3) at least 50% time spent providing direct patient care; 4) at least 50 patients with RA treated per month; 5) at least 25 treated with biologic therapy; and 6) not employed by or</li> </ul>	<ul style="list-style-type: none"> <li>Route of administration (intravenous infusion (IV) only, subcutaneous injection (SQ) only, both IV and SQ, neither)</li> <li>Attributes of biologic therapies (self-injection: every 4 weeks or monthly; self-injection: every 2 weeks; self-injection: once a week; self-injection: twice a week; IV: taking 30 minutes, every 8 weeks; IV: taking 30 minutes, every 4 weeks; IV: taking 1 hour, every 4 weeks; IV: taking 2 hours, every 8 weeks; IV: taking 2 hours, every 4 weeks; IV: two infusions taking 5 hours, separated by 2 weeks, every 16–24 weeks)</li> </ul>	<p>Preferences differed among patients with RA from rheumatologists' perceptions of these preferences for biologic therapy, including greater openness to intravenous infusion among patients than assumed by rheumatologists and relative lack of discussion about key aspects of biologic therapy perceived by patients. There is a need for more open communication about treatment options, which may encourage more appropriate, timely transition to biologic therapy.</p>

<p>providing consulting services to any pharmaceutical company and not working for government.</p> <ul style="list-style-type: none"> <li>- Sample size: 243 patients, 103 rheumatologists.</li> </ul>		<p>Two groups of patients with a diagnosis of RA and receiving two or more DMARDs were investigated. A large group of patients who had not used anti-TNF-<math>\alpha</math> drug were surveyed and a smaller group who had already received more than one anti-TNF-<math>\alpha</math> drug were interviewed.</p> <ul style="list-style-type: none"> <li>- Sample size: 109 patients (questionnaire survey), 7 patients (interviews).</li> </ul>	<p>Mixed methods, using a questionnaire survey and interviews</p>	<p>Find whether RA patients wished to participate in decisions about choosing an anti-tumor necrosis factor (TNF)-<math>\alpha</math> drug and the factors that influenced their choice.</p>	<p>RA patients demonstrate a clear treatment preference. Different factors influence patients who choose subcutaneous compared with intravenous medications. Many RA patients either wished to share in treatment decisions or relinquish responsibility to the health professional when choosing anti-TNF-<math>\alpha</math> therapy. Patients require reassurance and continuing dialog with clinicians to manage their condition optimally.</p> <ul style="list-style-type: none"> <li>- Mode of administration (subcutaneous, intravenous)</li> <li>- Side effects</li> <li>- Preparation of medicine needed (use of a ready to-use syringe with the correct dose: yes/no)</li> <li>- Drug errors</li> </ul>
<p>Constantinescu et al<sup>25</sup></p>	<p>Determine whether black and white RA patients differ in how they make trade-offs between the specific risks and benefits related to treatment.</p>	<p>Inclusion criteria were: 1) RA diagnosed by, and currently under the care of a rheumatologist; 2) a positive serum test for at least one of the RA-associated autoantibodies (rheumatoid factor or anti-cyclic citrullinated peptide); 3) self-identified as black or white; and 4) able to read and write English.</p> <ul style="list-style-type: none"> <li>- Sample size: 136 patients.</li> </ul>	<p>Adaptive conjoint analysis (ACA) questionnaire</p>	<p>Benefits (chance of remission, symptom improvement and radiographic progression)</p> <ul style="list-style-type: none"> <li>- Route of administration</li> <li>- Risks (injection reaction, nausea, lung or liver injury, tuberculosis, neurological disease and theoretical risk of cancer)</li> </ul>	
<p>Fraenkel et al<sup>25</sup></p>	<p>Examine patient trade-offs between specific drug characteristics, including expected benefits, risk of adverse effects and costs, and to ascertain individual patient preferences for specific DMARDs.</p>	<p>RA patients who had seen a rheumatologist for treatment of RA within the previous 12 months.</p> <ul style="list-style-type: none"> <li>- Sample size: 120 patients.</li> </ul>	<p>ACA questionnaire</p>	<p>Route of administration (one pill taken once a day in the morning, subcutaneous injection, intramuscular injection)</p> <ul style="list-style-type: none"> <li>- Experience (ie, the amount of experience doctors have with the drug)</li> <li>- Benefit (onset, chance of benefit and erosions)</li> <li>- Common reversible adverse events (injection reaction, rash, oral ulcers, alopecia, nausea and diarrhea)</li> </ul>	

(Continued)



Table S1 (Continued)

Publication	Objective(s)	Study design	Study population and sample size	Attributes (levels)	Conclusion
Goekoop-Ruiterman et al <sup>27</sup>	To determine treatment preferences among patients with recent onset RA participating in a randomized controlled trial (RCT) comparing four therapeutic strategies.	Retrospective RCT	<ul style="list-style-type: none"> <li>Inclusion criteria: 1) age <math>\geq 18</math> years; 2) recent onset of RA according to the ACR 1987 criteria; 3) disease duration <math>\leq 2</math> years; and 4) active disease with <math>\geq 6/66</math> swollen joints, <math>\geq 6/68</math> tender joints and either an erythrocyte sedimentation rate (ESR) <math>\geq 28</math> mm/h or a visual analog scale (VAS) global health <math>\geq 20</math> mm (on a scale of 0–100 mm where 0 = best and 100 = worst).</li> <li>Sample size: 440 patients.</li> </ul>	<ul style="list-style-type: none"> <li>Less common, but potentially more serious, adverse effects (cancer, renal toxicity, hepatic toxicity and pneumonitis)</li> <li>Costs</li> <li>Improvement general health (yes/no)</li> <li>Acceptable current state of health (yes/no)</li> <li>Kind of treatment (one well known DMARD, a combination of well-known DMARDs without Prednisone, a combination of well-known DMARDs with Prednisone, a combination of well-known DMARDs with a new intravenous drug (Infliximab))</li> <li>Rapid relief of symptoms (yes/no)</li> <li>Going to the hospital for intravenous treatment (yes/no)</li> </ul>	The implementation of new treatment strategies for patients with RA is primarily based on the comparison of treatment effects, side effects and costs. The negative perception of Prednisone and the positive perception of Infliximab are unmistakable.
Hazlewood et al <sup>15</sup>	<ul style="list-style-type: none"> <li>To quantify the preferences of patients with early RA with the benefits and harms of DMARDs.</li> <li>Identify any subgroups of patients with different treatment preferences.</li> </ul>	DCE	<ul style="list-style-type: none"> <li>Consecutive patients with early RA (<math>&lt; 2</math> years since diagnosis by a rheumatologist) from early RA clinics.</li> <li>Sample size: 152 patients.</li> </ul>	<ul style="list-style-type: none"> <li>Chance of a major symptom improvement by 6 months (30 of 100 people, 50 of 100 people, 70 of 100 people)</li> <li>Chance of serious joint damage by 10 years (2 of 100 people, 15 of 100 people, 30 of 100 people)</li> <li>Chance of stopping the medication due to a side effect by 6 months (2 of 100 people, 10 of 100 people, 20 of 100 people)</li> <li>How you take the medication(s) (one medication: daily pills, one medication: weekly tablets, one medication: weekly injections, two medications: weekly tablets and daily tablets (two pills), two medications: weekly tablets and</li> </ul>	On average, patients with early RA were risk tolerant, but important differences in preferences were identified. In particular, a subgroup of patients may prefer to avoid treatments with a possible increased risk of cancer/infection if other effective options are available.

<p>injection at home every week, two medications: weekly tablets and intravenous infusion in a clinic or hospital every 8 weeks, three medications: weekly tablets and daily tablets (six pills))</p> <ul style="list-style-type: none"> <li>- Possible rare lung or liver reaction (need for regular blood work) (yes/no)</li> <li>- Need for regular eye exams (yes/no)</li> <li>- Small risk of serious infections and possible increased risk of certain cancers (yes/no)</li> <li>- Need to limit alcohol (yes/no)</li> </ul>		<p>The majority of urban RA patients treated with biologics preferred their current route of administration, but reported a preference for a lower treatment frequency. The majority of urban RA patients not currently treated with a biologic and the health professionals in rheumatology favored SCH over IVC with a low treatment frequency. Safety issues were important to patients who preferred IVC.</p>
<p>injection at home every week, two medications: weekly tablets and intravenous infusion in a clinic or hospital every 8 weeks, three medications: weekly tablets and daily tablets (six pills))</p> <ul style="list-style-type: none"> <li>- Possible rare lung or liver reaction (need for regular blood work) (yes/no)</li> <li>- Need for regular eye exams (yes/no)</li> <li>- Small risk of serious infections and possible increased risk of certain cancers (yes/no)</li> <li>- Need to limit alcohol (yes/no)</li> </ul>	<p>Route and frequency of administration (intravenous infusion at the outpatient clinic (IVC) every 8 weeks, IVC every 4 weeks, two IVC, two weeks apart, once a year, subcutaneous self-injection at home (SCH) once a week, SCH every other week, SCH once a month, and SCH with the help of a home nurse once a week, every other week, or once a month)</p> <ul style="list-style-type: none"> <li>- Transportation time to the hospital</li> <li>- Effects</li> <li>- Adverse effects</li> <li>- Financial costs</li> </ul>	<p>The majority of urban RA patients treated with biologics preferred their current route of administration, but reported a preference for a lower treatment frequency. The majority of urban RA patients not currently treated with a biologic and the health professionals in rheumatology favored SCH over IVC with a low treatment frequency. Safety issues were important to patients who preferred IVC.</p>
<p>injection at home every week, two medications: weekly tablets and intravenous infusion in a clinic or hospital every 8 weeks, three medications: weekly tablets and daily tablets (six pills))</p> <ul style="list-style-type: none"> <li>- Possible rare lung or liver reaction (need for regular blood work) (yes/no)</li> <li>- Need for regular eye exams (yes/no)</li> <li>- Small risk of serious infections and possible increased risk of certain cancers (yes/no)</li> <li>- Need to limit alcohol (yes/no)</li> </ul>	<p>Route and frequency of administration (intravenous infusion at the outpatient clinic (IVC) every 8 weeks, IVC every 4 weeks, two IVC, two weeks apart, once a year, subcutaneous self-injection at home (SCH) once a week, SCH every other week, SCH once a month, and SCH with the help of a home nurse once a week, every other week, or once a month)</p> <ul style="list-style-type: none"> <li>- Transportation time to the hospital</li> <li>- Effects</li> <li>- Adverse effects</li> <li>- Financial costs</li> </ul>	<p>The majority of urban RA patients treated with biologics preferred their current route of administration, but reported a preference for a lower treatment frequency. The majority of urban RA patients not currently treated with a biologic and the health professionals in rheumatology favored SCH over IVC with a low treatment frequency. Safety issues were important to patients who preferred IVC.</p>

(Continued)

Table S1 (Continued)

Publication	Objective(s)	Study design	Study population and sample size	Attributes (levels)	Conclusion
Lisicki and Chu <sup>28</sup>	To identify the considerations that are most important to patients and physicians when deciding to initiate biologic response modifiers (BRM) therapy for RA.	Online survey	<ul style="list-style-type: none"> <li>Eligibility criteria patients: 1) US resident; 2) ≥ 18 years; 3) physician-diagnosed with moderate to severe RA; and 4) taking qualified RA medications for ≥ 3 months.</li> <li>Sample size: 729 patients.</li> </ul>	<ul style="list-style-type: none"> <li>Safety</li> <li>Efficacy</li> <li>Physician's experience with the product</li> <li>Method of administration</li> <li>Dosing frequency (tied)</li> <li>Physician's personal preference for the product</li> <li>Costs</li> <li>Years on the market</li> <li>Patient support programs</li> </ul>	<p>These data show that physicians and patients share similar concerns when deciding to initiate BRM therapy, although patients ranked safety as their first consideration, whereas physicians ranked efficacy first. Therefore, patient counselling and education regarding adverse events may be helpful when recommending BRM treatment.</p>
Louder et al <sup>33</sup>	To ascertain relative patient preferences associated with the route of administration and other attributes of biologic DMARDs and targeted synthetic DMARDs in the treatment of patients with RA.	Cross-sectional postal survey, using a complete blood count (CBC) analysis	<ul style="list-style-type: none"> <li>Inclusion criteria: 1) aged 21 to 80 years at the time of survey administration; and 2) currently enrolled in a fully insured Humana commercial health plan with medical and pharmacy benefits and have had at least 2 RA related medical claims in the previous 12 months, at least 30 days apart, as identified by International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code 714.0 (RA).</li> <li>Exclusion criteria: 1) resided in a nursing home; 2) eligible for low-in-come subsidies; and 3) evidence of a paid claim for Tofacitinib or for a biologic DMARD indicated for RA, psoriasis or ankylosing spondylitis (AS) at any time during their health plan enrollment before the mailing of the survey.</li> <li>Sample size: 380 patients.</li> </ul>	<ul style="list-style-type: none"> <li>Route of administration (oral, by self-injection, by infusion)</li> <li>Frequency of administration (twice daily, once weekly, every other week, once every 8 weeks)</li> <li>Chance of serious side effects (4 of 100 people, 6 of 100 people, 8 of 100 people)</li> <li>Monthly costs to you (commercial) (\$25 copay, \$50 copay, \$75 copay)</li> <li>Ability to reduce daily joint pain and joint swelling (50 of 100 people, 52 of 100 people, 54 of 100 people, 58 of 100 people)</li> <li>Improvement in ability to perform daily tasks and activities (32%, 33%, 34%, 36%)</li> <li>Medication burden (take with another medication) (yes/no)</li> </ul>	<p>The attribute with highest score on importance was the route of administration. The majority preferred the oral route of administration over other routes.</p>

<p>Nolla et al<sup>34</sup></p>	<p>To define the importance of values (preferences) assigned to the attributes of biological agents by Spanish patients with the main rheumatic diseases RA, AS and psoriatic arthritis (PsA), and by their rheumatologists.</p>	<p>Observational cross-sectional study based on a conjoint analysis methodology (rank-based full-profile conjoint)</p>	<ul style="list-style-type: none"> <li>- Inclusion criteria patients: 1) diagnosed with RA, AS or PsA at least 2 years prior to their inclusion; and 2) currently or previously (<math>\leq 1</math> year ago) receiving biological agents for a minimum of 1 year.</li> <li>- Exclusion criteria patients: 1) a need to translate the questionnaire; 2) coexistence of the studied rheumatic diseases; 3) incapacity to participate due to clinical, physical, or intellectual factors according to clinician judgement; and 4) currently taking part in a clinical trial.</li> <li>- Inclusion criterion rheumatologists: at least three years' experience in the use of biological agents.</li> <li>- Exclusion criterion rheumatologists: practice in private sector.</li> <li>- Sample size: 488 patients, 136 rheumatologists.</li> </ul>	<ul style="list-style-type: none"> <li>- Administration method (subcutaneous self-administration at home, intravenous administration by a healthcare professional at the hospital)</li> <li>- Risk of adverse events (high risk of adverse events, low risk of adverse events)</li> <li>- Pain relief and improvement in functional capacity (yes/no)</li> <li>- Duration of effect (time until perceiving the need for a new dose) (1 week, 2 weeks, 4 weeks, 8 weeks)</li> </ul>	<p>Preferences for biological agents were similar for rheumatologists and Spanish patients with rheumatic diseases, preferring medication that relieves pain and improves ability to perform daily activities, with a low risk of adverse events, self-administered at home subcutaneously, and with a greater time before perceiving the need for a new dose. Although efficacy and safety are key aspects for participants, both the frequency and method of administration play an important role as attributes for biological agents.</p>
<p>Poulos et al<sup>14</sup></p>	<p>To quantify the rate at which RA patients are willing to trade off between treatment duration and frequency.</p>	<p>DCE (online)</p>	<ul style="list-style-type: none"> <li>- Respondents from the Knowledge Networks (KN) online panel and the RA Information Service and Education (RISE) group. Inclusion criteria: 1) age <math>\geq 18</math> years; 2) capable of reading and understanding English; 3) living in the USA; 4) having a self-reported physician diagnosis of RA; and 5) having moderate to severe RA symptoms (RAPID-3 score of 6 or higher).</li> <li>- Sample size: 849 patients.</li> </ul>	<ul style="list-style-type: none"> <li>- Chance of medicine working well (75 of 100 patients (75%), 60 of 100 patients (60%), 40 of 100 patients (40%))</li> <li>- Mode of administration (injection at home, infusion at a doctor's office or clinic)</li> <li>- Time needed for infusion (no time (injection at home), 30 minutes (0.5 hours), 1 hour, 2 hours, 4 hours)</li> <li>- How often injections/infusions are taken (2 treatments every week (104 times per year), 1 treatment every 2 weeks)</li> </ul>	<p>Patients would be willing to accept treatments with lower efficacy or greater risks of side effects if these treatments had lower treatment duration or frequency. Further, a 1-hour reduction in duration is more important than reducing the frequency by 1 treatment per year. The importance of changes in annual treatment frequency depends on treatment duration and vice versa.</p>

(Continued)

**Table S1** (Continued)

Publication	Objective(s)	Study design	Study population and sample size	Attributes (levels)	Conclusion
Scarpato et al <sup>30</sup>	To evaluate RA patients' preferences for treatment (intravenous or subcutaneous) based on the route and frequency of administration of different anti-TNF- $\alpha$ drugs.	Cohort study with a questionnaire survey	<ul style="list-style-type: none"> <li>- Inclusion criteria: 1) age &gt; 18 years; 2) able to sign written informed consent and complete the questionnaire;</li> <li>3) diagnosis of RA according to the 1987 ACR criteria; and</li> <li>4) eligibility for an anti-TNF-<math>\alpha</math> drug.</li> <li>- Exclusion criteria: 1) previous therapies with an anti-TNF-<math>\alpha</math> drug; and 2) administration of any other subcutaneous or intravenous drugs at regular intervals (for instance insulin, desensitization therapies and heparin).</li> <li>- Sample size: 802 patients.</li> </ul>	<p>(26 times per year), 2 treatments 2 weeks apart every 6 months (4 times per year))</p> <ul style="list-style-type: none"> <li>- Chance of immediate serious treatment reaction (1 of 100 patients (1%), 10 of 100 patients (10%), 25 of 100 patients (25%))</li> <li>- Chance of immediate mild treatment reaction (1 of 100 patients (1%), 10 of 100 patients (10%), 25 of 100 patients (25%))</li> </ul>	<p>The preference towards intravenous and subcutaneous routes identifies different patient profiles: some patients choose intravenous for safety, rapidity of action and reassurance, whereas some prefer subcutaneous for convenience and confidence with self-administration.</p>



**Table S2** Patients' rankings of attributes during the focus groups

Ranking	Attribute
1	Risk of cancer <sup>a</sup>
2	Risk of liver injury <sup>a</sup>
3	Chance of efficacy <sup>a</sup>
4	Risk of joint damage
5	Onset of action <sup>a</sup>
6	Risk of serious infections <sup>a</sup>
7	Knowledge about long-term consequences of DMARD use
8	Risk of gastrointestinal complications
9	Route of administration <sup>a</sup>
10	Years of experience with DMARD to treat RA
11	Risk of mouth ulcers
12	Risk of headache or dizziness
13	Location of administration
14	Frequency of administration <sup>a</sup>
15	Combination therapy
16	Risk of skin rash
17	Time needed for infusion
18	Risk of hair loss
19	Chance of injection side reaction
20	Required storage conditions
21	Preparation of DMARD needed
22	Costs

**Notes:** Rank 1 means most relevant and rank 22 means least relevant. <sup>a</sup>This attribute was eventually included in the DCE.

**Abbreviations:** RA, rheumatoid arthritis; DCE, discrete choice experiment; DMARD, disease-modifying antirheumatic drug.

## Patient Preference and Adherence

Dovepress

### Publish your work in this journal

Patient Preference and Adherence is an international, peer-reviewed, open access journal that focuses on the growing importance of patient preference and adherence throughout the therapeutic continuum. Patient satisfaction, acceptability, quality of life, compliance, persistence and their role in developing new therapeutic modalities and compounds to optimize

clinical outcomes for existing disease states are major areas of interest for the journal. This journal has been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/patient-preference-and-adherence-journal>