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Patients' Willingness to Trade off Between the Duration and Frequency of Rheumatoid Arthritis Treatments

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SIGNIFICANCE AND INNOVATIONS

- This study quantifies the rate at which rheumatoid arthritis (RA) patients in the United States are willing to trade off between the time required to administer treatment (treatment duration) and treatment frequency.
- The marginal utility of, or relative preference for, changes in annual treatment frequency depends on the treatment duration and vice versa.
- The results indicate that respondents would accept treatments with lower efficacy and greater safety risks to get lower treatment duration and frequency.
- Previous research has linked preferences to likely adherence. Thus, providing patients with RA treatments requiring reduced duration and frequency could improve adherence and health outcomes.

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ABSTRACT

Objectives: Biologic treatments for rheumatoid arthritis (RA) vary widely in both the time required to administer treatment and treatment frequency. This study aimed to quantify the rate at which RA patients are willing to trade off between the time required to administer treatment (duration) and treatment frequency.

Methods: Respondents with a self-reported physician diagnosis of moderate to severe RA completed a online discrete choice experiment survey (also known as conjoint-analysis). Respondents were presented with a series of treatment-choice questions. Each hypothetical treatment included six attributes: response rate, mode of administration, treatment duration, treatment frequency, and the risks of immediate, mild and serious treatment reactions. Preference weights, also called marginal utilities or relative importances, were estimated using mixed-logit methods and then used to calculate the marginal rates of substitution between attributes, including treatment duration and treatment frequency.

Results: Among the 901 respondents, 505 were in the RA Information, Service, and Education group (www.risesupport.com), and 396 were members of an online panel. The marginal utility of changes in treatment features was largest for a one-hour change in treatment duration, while a one-unit change in the annual frequency of treatment was the second least important change. The marginal utility of changes in annual treatment frequency depends on the treatment duration and vice versa.

Conclusions: Respondents would accept treatments with lower efficacy and greater risk to achieve lower duration and frequency. Previous studies have linked patient preferences to

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treatment adherence, suggesting that reductions in duration or frequency could improve adherence and health outcomes.

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Key indexing terms: patient preferences, rheumatoid arthritis, conjoint analysis, discrete-choice experiment, biologic treatments

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Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by inflammation of the synovial lining of the joints.[1] An estimated 1.5 million adults in the United States have RA, or between 0.5% and 1% of the nation's adult population, and the prevalence among women is 2-3 times that among men.[2,3] Without treatment, RA leads to joint destruction and profound morbidity and mortality.[1]

Treatment options for RA include nonsteroidal anti-inflammatory drugs, glucocorticoids, traditional disease-modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs.[4] Biologic DMARDs are very effective in treating RA and are commonly used for patients with suboptimal response or intolerance to traditional DMARDs.[4]

Due to work, children, and other competing responsibilities, RA patients often have limited time to spend on administering RA treatments. Some biologic DMARDs are given infrequently but require half of a person's work day to administer (e.g., rituximab requires two 4-hour infusions administered 2 weeks apart every 24 weeks), whereas other treatments are of shorter duration but require more frequent administration (e.g.,adalimumab is administered via injection once every two weeks). Several studies establish a link between patient preferences and adherence to biologic DMARDs for RA.[5] One study [6] reports that the majority of nonadherent RA patients have concerns about their medication, suggesting that understanding patient preferences for RA treatment can help to improve treatment adherence and health outcomes.

Three previous conjoint analyses of patient preferences for RA treatments found that the mode and frequency of administration matter to RA patients and may be at least as important as treatment response rate and the risk of treatment side effects.[7-9] All three of these studies measured preferences for combinations of mode of administration and treatment frequency, but

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none of the studies evaluated patients' preferences for treatment duration or their willingness to trade off between treatment duration and frequency. Therefore, the objective of this study is to quantify the rate at which RA patients are willing to trade off between treatment duration and frequency.

MATERIAL AND METHODS

Study Design

The methodological approach employed was a discrete choice experiment (DCE) (also known as a choice-format conjoint analysis). DCE is based on the assumption that patients' preferences for treatment are a weighted function of treatment attributes (e.g., efficacy, safety, and convenience), where the weights indicate the strength of preference for an attribute level relative to other levels and can be used to calculate the rate at which patients would be willing to accept tradeoffs among attributes. In a DCE, patients are presented with a series of treatment-choice questions in which patients choose their preferred treatment from a set of hypothetical treatment alternatives, each with different levels of the attributes. Statistical analysis of the pattern of the stated choices reveals the rate at which patients are willing to trade off among the attributes and the relative preference for, or marginal utility of, changes in each attribute.

Six attributes were selected based on the study objective and a review of studies of patient preferences for RA treatments. The attributes were chosen to include attributes that previous studies indicated were important to RA patients, and treatment administration attributes that differ between existing biologic DMARDs. Attributes included treatment response rate, mode of administration, treatment duration, treatment frequency, and the risks of immediate, mild and severe treatment reactions (Table 1). The ranges of attribute levels were selected to

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span the ranges that described existing RA treatments and to include the levels over which patients were willing to accept tradeoffs among attributes. The attribute levels describing existing treatments were developed based on a review of product labels and clinical studies. Pretest interviews determined the range of levels over which patients were willing to accept tradeoffs by posing a series of follow-up questions after selected treatment-choice questions. The questions explored the attribute levels that would induce respondents to change their treatment choice. Because respondents are typically willing to accept trade-offs over a broader range than is observed in existing treatments, the attribute levels in the study may include levels not observed in available therapies.

In each choice question, respondents were asked to indicate which of two hypothetical RA treatments they would choose if these were the only two treatments available (Figure 1). The combinations of attributes and levels that defined each treatment pair were determined by an experimental design, which was developed consistent with recent guidance.[10] We used the SAS implementation of a commonly used D-optimal algorithm to construct a fractional factorial experimental design.[11,12] D-optimality is a measure of the efficiency of an experimental design, with efficient designs maximizing the precision of estimated choice-model parameters for a given number of choice questions. Developing a D-efficient design requires identifying a subset of the full-choice design of all meaningful attribute-level combinations placed into pairs of treatment alternatives. The statistical properties of the design are known, which allows for the estimation of parameters of interest.[11,12]

The selected experimental design defined 120 hypothetical RA treatment pairs. Previous studies have found that the quality of responses to choice questions declines when the number of choice tasks leads to fatigue or cognitive burden.[13-15] To reduce potential measurement error

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introduced by cognitive burden, the 120 paired comparisons in the experimental design were divided into 12 survey versions, each containing 10 treatment-choice questions. Each patient was randomly assigned to one of the 12 versions and the order of the treatment-choice questions within each version was randomized for each respondent.

The survey also collected information on the demographic characteristics, health history, and RA treatment experience of respondents. The survey was approved by RTI International's Office of Research Protection and Ethics (Research Triangle Park, North Carolina).

Study Subjects

The DCE was administered online by Knowledge Networks (KN) in March and April 2011. Respondents were recruited by email invitations to members of two groups: KN's online panel, a panel of US households accessible for online surveys; and the RA Information, Service, and Education (RISE) group (www.risesupport.com), an opt-in patient group. Respondents were required to be 18 years of age or older, to be capable of reading and understanding English, to be living in the United States, to have a self-reported physician diagnosis of RA, and to have moderate to severe RA symptoms. The Routine Assessment of Patient Index Data, Version 3 (RAPID3), a patient self-assessment of pain, function, and overall well-being, was used to screen for respondents with moderate to severe RA. The RAPID3 is measured on a 30-point scale, with scores of 6 through 11 indicating moderate RA, and scores of 12 or higher indicating severe RA.

The screening process differed between the two groups. Recruits from the KN online panel were screened by administering the RAPID3 to respondents meeting the remaining inclusion criteria and excluding respondents who had a RAPID3 score less than 6. Members of the RISE group completed the RAPID3 upon joining the RISE group. Email invitations were

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sent to a random sample of RISE members who had a RAPID3 score greater than or equal to 6 at the time they joined the RISE group. Recruits from RISE were then screened for the remaining inclusion criteria. All subjects provided online informed consent.

Statistical Analysis

The pattern of respondents' treatment choices was analyzed using a random-parameters logit (RPL or mixed logit) regression model. RPL accounts for the panel nature of the data, and respondent heterogeneity in preferences, and does not require the independence of irrelevant alternatives assumption.[16] In an RPL model, the dependent variable is treatment choice, and the explanatory variables are the attributes shown in Table 1. The resulting parameter estimate on each attribute level quantifies the marginal utility of a change in that attribute, which we refer to as the preference weight, or relative preference, for that attribute level.[16-18] Because all attributes, except for mode of administration (i.e., injections or infusions), have numeric levels, these attributes were specified as continuous variables. To empirically determine the appropriate functional form of each one of the continuous variables, we used a Box-Cox estimator, which approximates the functional form that provides the best model fit for each of the continuous variables.[19] These functional forms were then used in the RPL model. The parameter estimate for each of the attributes represented using a continuous variable represents the relative preference for a 1-unit change in the numeric value of the transformed attribute level.

Mode of administration was set equal to 1 if a treatment profile included injections and 0 if a treatment profile included infusions. Therefore, the parameter estimate for mode of administration indicates the relative preference for injections relative to infusions.

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Each attribute in the model had a random parameter assumed to be normally distributed. All analyses were conducted using NLOGIT 4.0 (Econometric Software, Inc., Plainview, NY, USA).

The estimated preference weights, or marginal utilities, were used to calculate the relative importance, or the the rates at which respondents would be willing to trade-off between changes in pairs of attributes. The relative importance is calculated as the ratio of two marginal utilities and is also known as the marginal rate of substitution (MRS). Further, the marginal utilities of treatment frequency and duration were also used to identify different combinations of frequency and duration among which patients are indifferent; that is, combinations of frequency and duration that are equally preferred. For example, a patient may be indifferent between a treatment with short duration and high frequency and a treatment with long duration and low frequency, all else equal. When the combinations of duration and frequency that are preferred equally by patients (that is, combinations among which patients are indifferent) are plotted on a graph, the resulting plot is known as an "indifference curve."

Using these indifference curves, the MRS between treatment frequency and duration is measured as the absolute value of the slope of the indifference curve at any given point along the curve. If preferences for changes in both frequency and duration are independent and linear over the range of levels included in the survey, the MRS between these two attributes is constant and the indifference curve will be a straight line. If preferences for changes in both frequency and duration are dependent on each other and/or are non-linear over the range of levels included in the survey, the MRS between these two attributes will be a function of the levels of frequency and duration at which the MRS is estimated and the indifference curve will be a curve rather than a straight line.

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RESULTS

Study Sample

KN sent e-mail invitations to 842 members of their online panel with self-reported RA. Of the 638 patients who responded (76%), 396 met the inclusion criteria and consented to participate in the survey. In addition, KN sent e-mail invitations to 12,175 members of the RISE group with RAPID3 scores of 6 or higher. Of the 519 patients who responded (4%), 498 consented to participate in the survey and met all inclusion criteria except 45 respondents that had a RAPID 3 score of less than 6 (indicating mild RA) at the time of the survey. These respondents had a RAPID 3 score greater than 6 at the time they enrolled in RISE. These respondents' data were not included in the analyses reported in this paper, though including these respondents did not significantly change the results (not shown). Seven respondents (0.1%) did not answer any choice questions and were deleted from the sample.

Table 2 presents the summary statistics for the 849 patients who completed the survey. At the time of the study, most patients (76%) used an oral prescription medication, 30% were receiving regular injections, and 17% were receiving regular infusions. Thirty-four percent had received regular injections previously and 30% had received regular infusions previously. Thirty-one percent of patients had a RAPID3 score that was greater than or equal to 6 and less than 12, indicating moderately severe RA. Most patients (70%) had a score of 12 or greater, indicating severe RA.

The majority of respondents (86%) provided the correct response to a risk grid comprehension question, indicating comprehension of the grids used to communicate the risk and treatment response rate levels. Thirteen respondents (1.5%) with no variation in their

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responses to the choice questions were deleted from the sample as this lack of variation suggested that these patients did not pay attention to the treatment-choice questions. Thus, 836 respondents were included in the analysis.

Preference Model and Weights

Table 3 presents the RPL regression results. A Box-Cox estimation indicated that the functional form that provided the best model fit for treatment frequency and response rate was a logarithmic specification.[i] Further, the Box-Cox estimator indicated that linear specifications of the other continuous treatment attributes (chances of mild or severe treatment reactions, and duration) provided the best fit. Based on pretest findings indicating that preferences for duration varied systematically with treatment frequency, we included an interaction term specified as the product of duration and frequency. The pretest findings did not support the inclusion of any other interaction terms in the preference model.

The magnitude of each parameter estimate indicates the weight respondents place on changes in the corresponding attribute (also referred to as relative preference or marginal utility). The positive coefficient on the logarithm of treatment response rate indicates that higher treatment response rates were preferred to lower treatment response rates. The negative coefficients on duration, the logarithm of annual frequency, and the risks of mild and severe treatment reactions indicate that lower levels of these attributes were preferred to higher levels of these attributes. The coefficient on mode of administration was not statistically significant (P=0.363).

The negative and statistically significant coefficient on the interaction between treatment duration and frequency indicates that the relative preferences for a 1-unit change in annual

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frequency is a function of the duration, and vice versa. When either annual frequency or duration decreases, the cumulative effect on preferences is the sum of the individual main effects on preferences for decreasing frequency or decreasing duration and the interaction effect.

The results presented in Table 4 were used to calculate the relative importance of, or the MRS between, attributes. For example, a 1-hour decrease in the duration of a quarterly infusion is approximately 5 times (=0.268/[3.277x(ln[61]-ln[60])]) as important as a 1-percentage point increase in the probability of response from 60% to 61% .

While Table 3 shows examples of the marginal utility of changes in duration and frequency, we consider additional examples in this section to illustrate the results as the initial duration and frequency vary. For example, when the initial duration is 2 hours and the frequency is 4 times per year, the marginal utility of a 1-hour decrease in duration is 0.268 (=[-0.264 x -1 hour duration]+[-0.001 x -1 hour duration x 4 times per year]). The marginal utilities of a 1 hour decrease in the duration of a 2-hour treatment administered 2, 12, and 104 times per year (twice per year, monthly, and twice per week administration) are 0.266, 0.276, and 0.372, respectively. Thus, the MRSs between the durations of these 2-hour treatments (administered twice per year, monthly, and twice per week) and the duration of a quarterly infusion are 0.99, 1.03, and 1.4, respectively. Further, because the main effect of frequency enters the model logarithmically, the relative preferences for changes in annual frequency also depend on the starting level of annual frequency. For example, when initial duration is 0.5 hours and the initial frequency is 12 times per year, the marginal utility of increasing frequency by 1 time per year is -0.043 (= [-0.526 x (ln(13) – ln(12)) + [-0.001 x 0.5 x (13-12)]). The marginal utilities of increasing annual frequency by 1 time per year (from 12 to 13) when the duration is 1, 2, and 4 hours are -0.043 (shown in Table 3), -0.044, and -0.46. Thus, the MRSs between an increase in frequency (from

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12 to 13) of a 1, 2, and 4 hour infusion and an increase in frequency of a half-hour treatment are 1.01, 1.04, and 1.1, respectively. Finally, the marginal utility for increasing the annual frequency of a half-hour treatment from 4 to 5 times per year is -0.118, which is 2.77 times more important than increasing the frequency of a half-hour infusion from 12 to 13 times per year. That is, the MRS between these changes is 2.77.

Indifference Curves

A set of indifference curves is presented in Figure 2. Each indifference curve represents a set of combinations of annual frequency and treatment duration (in hours) which are equally preferred by respondents (i.e., among which they are indifferent), all else equal. The indifference curves are nonlinear curves rather than straight lines because preferences for changes in annual frequency are non-linear and because preferences for changes in duration depend on the level of annual frequency and vice versa. In Figure 2, indifference curves that are lower or further to the left represent combinations of frequency and duration that are preferred to combinations on indifference curves that are higher or further to the right. For example, suppose one starts at X1 (duration of 4 hours and a frequency of 2 times per year) and moves to Y (increasing frequency to 4 times per year). Y is worse, and thus less preferred, than X1. Therefore, Y is on a higher indifference curve than X. By decreasing duration to 2.5 hours, we move from Y to X2. The loss experienced by increasing frequency (moving from X1 to Y) is exactly offset by the gain experienced by decreasing duration (moving from Y to X2) and patients prefer X1 and X2 equally. The MRS between duration and frequency between points X1 and X2 is approximated by the slope of the line between these two points and is thus 1.3 (=2/1.5) indicating that patients are willing to trade a reduction in duration of 1.5 hours for an increase in frequency of 2 times per year. Alternatively, this result can be viewed as indicating that if the duration of a treatment

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that occurs 4 times per year can be reduced from 4 hours to 2 hours patients would be better off than reducing the frequency of a 4-hour treatment from 4 times per year to 2.5 times per year.

DISCUSSION

To our knowledge, these results provide the first systematic quantification of the rate at which RA patients' in the US are willing to trade off treatment duration and frequency. In addition, this is the first DCE in a health application to present empirical results using indifference curves.

The marginal utilities reported in Table 3 indicate that the relative preference for a 1-hour change in duration (from 2 hours) of a quarterly infusion is more than 6 times greater than the relative preference for an increase in annual treatment frequency by one (from 12 times per year), about 5 times greater than the relative preference for a 1-percentage-point increase in treatment response rate (from 60% to 61%), and more than 3 times greater than the relative preference for a change in mode of administration (between injection and IV infusion). The relative preference for this change in hours required for treatment (from 2 hours to 1 hour) is also 12 and 2 times greater than the relative preferences for 1 percentage point changes in the chance of mild or serious treatment reactions, respectively.

The results indicated that the relative preferences for treatment duration depended on the level of annual treatment frequency and vice versa. These results are consistent with RA patients being concerned with the total amount of time spent receiving treatment. These results are consistent with previous studies' findings that treatment frequency and mode of administration may be at least as important as treatment response rate and the risk of treatment related side effects.[7-9] However, by varying frequency and duration independently in the experimental

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design, our study was the first that allowed the estimation of preferences for both of these treatment attributes.

Despite the increasing use of DCE in health applications to elicit preferences, this approach has several potential limitations. One inherent limitation is that the patients evaluated hypothetical RA treatment profiles that do not have the same clinical consequences of actual choices. We attempted to minimize the potential for hypothetical bias by offering treatments that mimic real-world tradeoffs as closely as possible. The majority of respondents answered questions about risk grid comprehension correctly and the preference weights are ordered, suggesting that respondents paid attention to the survey questions and information. Nevertheless, actual treatment choice decisions may differ from the stated choices of respondents provided during the interviews because of the influence of treatment attributes that were not included in the study (e.g., treatment cost) as well as other influences on decisionmaking (e.g., lifestyles).

Another limitation is that respondents' self-reported diagnoses of RA were not independently verified. Nevertheless, we followed up the self-report with questions on symptoms and severity of symptoms— pain, function, and overall well-being – and only included respondents in the sample if they reported symptoms that were consistent with moderate to severe RA.

As in any survey-research study, we need to be mindful of sample representativeness as a potential study limitation. The study sample is small relative to the population and it was drawn from two different sources: KN's online panel and the RISE group. KN's panel is a nationally representative panel of US households recruited for the purpose of completing online surveys.

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While KN's panel is representative of the US population, the RA sample is not necessarily representative of the RA population in the US.

The RISE group is a group that RA patients join in order to access information about RA treatments and they agree to be contacted as a condition of membership. It may not be representative of the US population. The response rate for the sample recruited from the RISE group was lower than the response rate for the sample recruited from KN's panel because RISE members are not engaged for the purpose of participating in surveys. We cannot fully judge how representative our sample was of people with RA in the US or whether our results are generalizable to all people with RA in the US.

CLOSING STATEMENT

The results indicate that 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. Previous research has linked preferences to likely adherence. Thus, providing patients with RA treatments requiring reduced duration and frequency could improve adherence and health outcomes.

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[i] These logarithmic specifications indicate that preferences for increases in response rate increase at a decreasing rate (i.e., a one percentage point increase in response rate is more important when the initial response rate is lower) and preferences for decreases in frequency increase at an increasing rate (i.e., a reduction in frequency increases in importance when the initial frequency is lower).

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Table 1. Treatment Attributes and Levels[a]

Treatment Attribute	Levels
Chance that the medicine will work well	• 75 out of 100 patients (75%) • 60 out of 100 patients (60%) • 40 out of 100 patients (40%)
The way you take the medicine (mode of administration)	• Injection at home • Infusion at a doctor's office or clinic
Time needed for infusion	• No time (injection at home)[b] • 30 minutes (0.5 hours) • 1 hour • 2 hours • 4 hours
How often you take injections or infusions	• Two treatments every week *(104 times per year)* • One treatment every 2 weeks *(26 times per year)* • One treatment every month *(12 times per year)* • Two treatments 2 weeks apart every 6 months *(4 times per year)*
Chance of an immediate, serious treatment reaction	• 1 out of 100 patients (1%) • 10 out of 100 patients (10%) • 25 out of 100 patients (25%)
Chance of an immediate, mild treatment reaction	• 1 out of 100 patients (1%) • 10 out of 100 patients (10%) • 25 out of 100 patients (25%)

[a] Respondents were told to assume that the cost of RA medicines and co-pays related to RA treatments were covered by health insurance.

[b] In the analysis, this attribute was defined as time required to administer treatment, rather than time needed for infusion. The injection at home level was assigned a time of 10 minutes.

Table 2. Sample Characteristics

Characteristic	Frequency (Percentage)
Age group (years)	
18-24	12 (1.4%)
25-34	25 (2.9%)
35-44	84 (9.9%)
45-54	213 (25.1%)
55-64	315 (37.1%)
65+	200 (23.6%)
Sex	
Male	217 (25.6%)
Female	631 (74.4%)
Race/ethnicity	
White, non-Hispanic	663 (78.1%)
Black, non-Hispanic	86 (10.1%)
Other, non-Hispanic	22 (2.6%)
Hispanic	42 (5.0%)
2+ races, non-Hispanic	36 (4.2%)
Education level	
Less than high school	48 (5.7%)
High school	187 (22.1%)
Some college	379 (44.7%)
Bachelor's degree or higher	233 (27.5%)
Metropolitan area	
Non-metropolitan	250 (29.6%)
Metropolitan	595 (70.4%)
Employment status	
Working – as a paid employee	256 (30.2%)
Working – self-employed	42 (5.0%)
Not working – on temporary layoff from a job	4 (0.5%)
Not working – looking for work	37 (4.4%)
Not working – retired	203 (24.0%)
Not working – disabled	269 (31.8%)
Not working – other	36 (4.3%)

Characteristic	Frequency (Percentage)
Household income level	
Less than $25,000	234 (28.5%)
$25,000-$49,999	235 (28.6%)
$50,000-$74,999	142 (17.3%)
$75,000-$99,999	92 (11.2%)
$100,000 or more	119 (14.5%)

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Table 3. Results of Random-Parameters Logit Analysis of RA Treatment Choice Data

Variable	Coefficient	Standard Error	P-value	Marginal Utility
Mode of treatment (=1 if injection, =0 if infusion)	0.083	0.091	0.363	0.083[a]
Chance of Immediate, Mild Treatment Reaction (percent)	-0.022	0.003	0.000	-0.022[b]
Chance of Immediate, Severe Treatment Reaction (percent)	-0.123	0.007	0.000	-0.123[b]
Ln(Treatment Response Rate)	3.277	0.1715	0.000	0.054[c]
Duration of Treatment (hours) X Annual treatment frequency[d]	-0.001	0.001	0.060	
Duration of Treatment (hours)	-0.264	0.034	0.000	-0.276[e]
Ln(Annual Treatment Frequency)	-0.526	0.042	0.000	-0.043[f]

[a] Relative preference for an RA treatment administered by injection instead of an RA treatment administered by infusion.

[b] Relative preference for a 1-percentage-point increase in the probability of a treatment reaction.

[c] Relative preference for a 1 percentage-point increase in the rate of treatment response from 60% to 61%.

[d] This interaction term is the product of the treatment duration (in hours) and the annual treatment frequency.

[e] Relative preference for a 1-hour increase in the duration of treatment when frequency = 12 time per year. The marginal effects of changes from different levels of duration and frequency are described in the text.

[f] Relative preference for a 1-unit increase in the frequency of treatment when initial frequency = 12 times per year and duration equals 0.5 hours. The marginal effects of changes from different levels of duration and frequency are described in the text.

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Figure 1. Example Choice Question

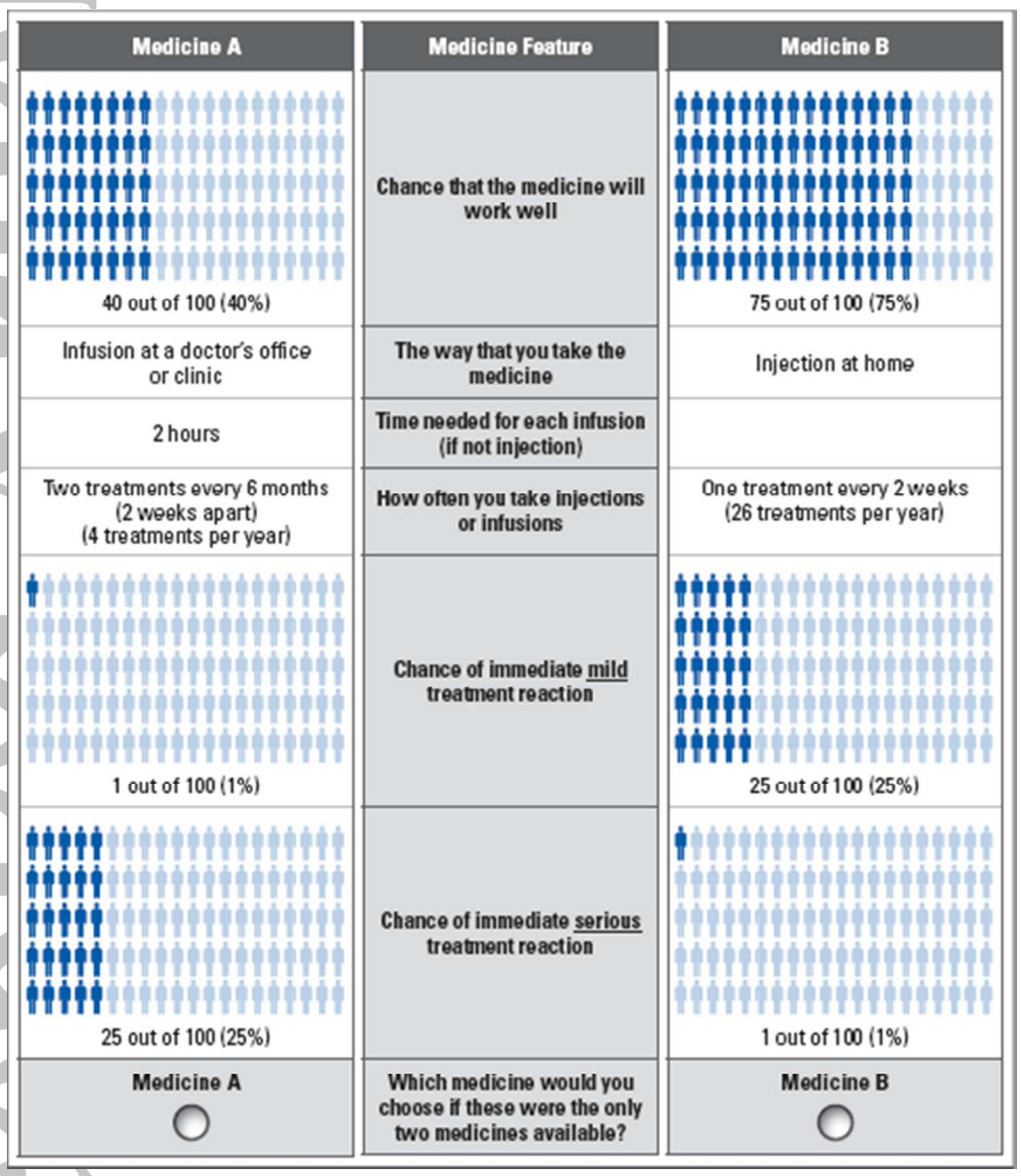
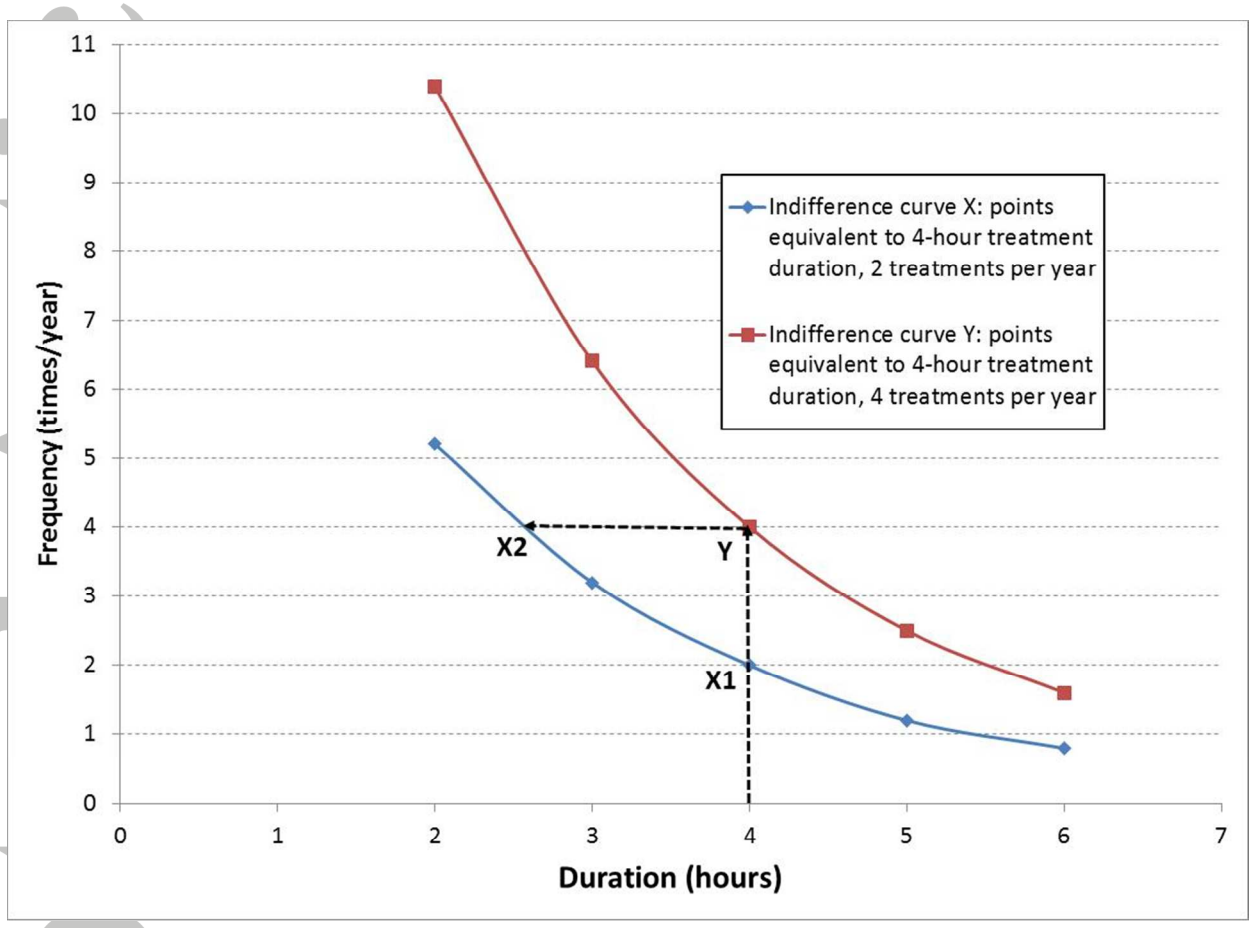


Figure 2. Indifference Curves between Duration of Treatment (in Hours) and Annual Frequency of Treatments



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