An implantable device to treat multiple sclerosis: A discrete choice experiment on patient preferences in three European countries

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ARTICLE INFO

Keywords:
Multiple sclerosis
Medical device
Patient preferences
Discrete choice experiment
Disease-modifying treatment

ABSTRACT

Background: Persons with multiple sclerosis (MS) take their treatment via pills, injections or infusions. A novel mode of disease-modifying treatment administration, an implantable device, is under development. This study determined MS patient preferences for three modes of first-line treatment administration (implant, pills, injections), and trade-offs regarding treatment characteristics.

Methods: A survey including a discrete choice experiment was conducted among MS patients in the Netherlands, France, and the United Kingdom. Respondents had to repeatedly choose between various treatment scenarios with four treatment characteristics: risk of relapse, reduction of disease progression, risk of side effects and mode of administration. Data was analysed using a panel latent class logit model.

Results: Based on the preferences of 753 MS patients (response rate 7%: 753/11202), two latent classes were identified (class probability of 74% vs 26%). Persons with relapsing-remitting MS and who administered medication via injections generally preferred any treatment over no treatment. Patients who could walk without an aid were more likely to prefer no treatment. Reducing disease progression was the most important treatment characteristic class 1. Mode of administration was the most important characteristic in class 2. Patients were willing to accept an increase in risk of relapse and disease progression to get their treatment via an implant rather than injections. Predicted uptake was the highest for the implant, followed by pills, injections, and no treatment.

Conclusion: We found that a drug-delivery implant could be a potential addition to the MS treatment landscape: MS patients are willing to trade-off risk of relapse and disease progression for an implant, and predicted uptake for an implant is relatively high.

1. Introduction

Multiple sclerosis (MS) is an invalidating disease affecting 2.8 million people worldwide [1]. MS has a chronic disease progression, which is immune-mediated and causes demyelination of the central nervous system affecting young adults, primarily women. The presentation of MS varies dependent on the location of the lesions and progression of the disease. Clinical features include physical dysfunctions (such as mobility and sensory problems) and cognitive decline [2]. Patients can progress from a single clinical event suggestive of MS (a clinically isolated syndrome; CIS) into relapsing-remitting MS (RRMS) [2]. Roughly 85% of patients are diagnosed with RRMS which is characterised by relapses (i.e. neurological dysfunctions) with full or partial recovery. The remaining patients may have disease progression from onset (diagnosed with primary progressive MS: PPMS) or have disease progression after having RRMS (diagnosed with secondary progressive MS: SPMS) [2].

The current treatment landscape is diverse and patients can be treated with multiple first- and second-line disease-modifying treatments (DMTs) that can be either injected, taken orally, or via infusion therapy [3]. However, DMTs are not able to cure MS. DMTs may reduce disease progression and relapse rate, are associated with various adverse events and each mode of administration has its own frequency of administration [3]. Consequently, patients have the difficult task of trading-off these different aspects of the therapy once deciding on starting a DMT.
Preference studies allow researchers to quantify patient preferences towards treatment decisions, thereby identifying the relative importance of health outcomes related to such a treatment decision [4]. As such, patient needs can be quantified and analysed. Stated preference (SP) studies, such as discrete choice experiments (DCEs), have gained popularity within the field of MS [5]. When performing a DCE, patients are asked to evaluate hypothetical MS treatment profiles based on a set of characteristics of treatment (attributes) and variants of these characteristics (attribute levels). Systematic reviews on this topic have identified that patients have a preference for treatments with a low risk of side-effects and treatments that delay disease progression along with reducing relapses. Moreover, patients prefer oral and infusion modes of administration over injections [6,7].

The Optogenery consortium, a European Horizon 2020 project, is developing a novel mode of first-line DMT administration for MS patients [8,9]. The Optogenery drug delivery implant releases beta-interferon (INF-β) into the body. The treatment is generated by genetically modified cells that produce INF-β confined within a chamber sealed by a porous membrane, which allows the device to be easily implanted or removed [9]. The implant is a new mode of administration and can potentially replace standard injectable first-line INF-β delivery. Since this implant may possibly be an addition to the current treatment landscape within the field of MS, it is expected that patients will face tough trade-offs concerning the new mode of administration, which makes it an interesting area for research into patient preferences. Furthermore, patient preference information can inform about the (unmet) needs of patients, guide the product development, cost-effectiveness analysis and market authorisation [10–12]. As such, the implant can be tailored to the needs of the patient, which may enhance patient satisfaction, lead to better health and more efficient healthcare systems [13].

The results of this study are of relevance for healthcare professionals, persons involved in medical technology development, and policy makers. Patient preference information may help healthcare professionals improve the shared decision-making with patients since patient and healthcare professionals treatment preferences can differ substantially [14–18]. Also, patient preference information can guide and improve product development [19]. Since such a device is new and the therapy released by the implant is INF-β, it is of interest to examine the relative desirability of this mode of administration compared to standard modes of first-line administration options for RRMS patients with comparable efficacy and safety profiles (pills or injectable therapy). We choose to not include infusion therapy as a mode of administration because it is usually given as a second-line therapy [20,21]. To our knowledge, no preference study has been performed examining an implantable device within the MS treatment landscape. Hence, the aim of this study is to quantify patient preferences for three modes of treatment administration (implant, pills, injections) and assess which trade-offs patients with MS are willing to make regarding treatment characteristics.

2. Materials and methods

2.1. Discrete choice experiment

This study used an online survey containing a discrete choice experiment (DCE) to elicit patient preferences for attributes of MS therapies in three Western European countries (the Netherlands, France, and the United Kingdom). The three countries were chosen because of the high prevalence of MS in the three countries (1 in 700 persons have MS in the Netherlands and in France, and 1 in 500 persons have MS in the United Kingdom), while taking study feasibility into account (location of members of the Optogenery consortium) [22–24]. In DCEs, respondents choose between pairs of hypothetical treatment profiles, defined by their characteristics (attributes, such as risk of relapse) and with varying levels of that attribute (such as 30% or 70% less risk of relapse), in a series of questions, called choice tasks [4,25]. Each choice task consists of a prespecified number of alternative treatment profiles with varying attribute levels (see Fig. 1). By repeatedly presenting different treatment profiles in the choice tasks, and asking the respondent to choose the profile they most prefer, it is possible to determine the relative importance of the attributes (and levels) to one another [4]. Using statistical methods that have a foundation in random utility theory, a DCE enables empirically studying relative importance between treatment attributes, while also taking into account patient characteristics [26].

2.2. Attributes and levels

The attributes and attribute levels concerning MS treatment were derived from systematic literature reviews [6,7] and were verified (i.e. cross validated) during two focus group sessions with MS patients (N = 16) held in the Netherlands and by consulting two French MS specialists [27]. Efficacy and safety were important themes identified in the focus group sessions [27] and combined with the results of the systematic reviews [6,7] the following four attributes were identified: risk of relapse, reducing disease progression, risk of side effects, and mode of administration. The attribute levels were chosen to capture the range of plausible outcomes of DMTs currently available on the market and the assumed health outcomes of the implant. In addition to side effects of DMTs described by the Dutch pharmacotherapy guidelines [28] we also included an adverse event specifically related to the implant, namely post-operative wound infection. A full description of the attributes and its levels can be found in Table 1 and Appendix A.

2.3. DCE design and questionnaire

The questionnaire was designed and developed following good
research practices [25,29]. Presenting all the selected attributes and attribute levels to a respondent would result in an unfeasibly large number of alternatives to be evaluated by the respondent. Hence, to reduce the number of alternatives while still being able to estimate the parameters of interest in a reliable way, a subset of alternatives was selected using a Bayesian D-efficient design as generated by Ngene software [30,31]. To increase statistical efficiency of the Dutch design, prior estimates of the parameters were updated after the pilot data was collected (n = 100 respondents) [30]. The questionnaire in the United Kingdom and France contained the same updated design to eliminate possible differences in preference outcomes between the countries resulting from the design.

We created a design of 30 choice tasks that were divided into two blocks of 15 to reduce respondent burden. Thus, per questionnaire version each respondent was presented with 15 choice tasks rather than 30. Each choice task consisted of three alternatives: two alternatives (‘Treatment 1’ and ‘Treatment 2’) were characterised by a selection of attribute levels and the third alternative (‘No treatment’) allowed respondents not to choose any of the presented alternatives (opt-out). We included this opt-out alternative since – as in real-life – MS patients may actively choose not to take any DMTs. An example of a choice task can be found in Fig. 1.

In addition to the 15 choice tasks described above, the questionnaire contained questions about patient demographics, health status, numeracy skills [32,33] and health literacy [34,35]. Patient demographics were dichotomised for later analyses, for example into MS type (RRMS vs. CIS, PPMS and SPMS and ‘I don’t know’), treatment course (taking 1st-line injectable DMT vs not taking a 1st-line injectable DMT), partner (married and partnered vs. unmarried, divorced, and widowed) and higher education (university vs. primary, secondary, vocational/technical education and other). Health status was measured using the EuroQol 5 Dimensions questionnaire (EQ5D-5 L) using country specific tariffs [36–39]. Furthermore, respondents were asked whether they would or would not be interested in having the implant as a mode of administration. Finally, six concluding questions about perceived difficulty and length of the questionnaire and treatment options (5-point scale: strongly agree to strongly disagree), and six questions on the extent to which they believe the COVID-19 pandemic affected their responses were asked (5-point scale: no influence to extreme influence).

The questionnaire was pre-tested using the think-aloud method in four Dutch MS patients. They were asked to read and think aloud while completing the questionnaire [25]. The respondents indicated that the questionnaire was clear, the length was manageable, and that treatment trade-offs were accurately reflected.

After data collection was completed in the Netherlands, the questionnaire was translated to English and French. Translation to English was done by the researchers. Translation to French was done by a translation agency. Furthermore, native speakers working in health economics who were not involved in this study checked the translations and performed back and forward translation for the attributes and levels.

2.4. Data collection and study sample

Inclusion criteria were persons older than 18 years of age, diagnosed with MS (either CIS, RRMS, SPMS or PPMS), living in the Netherlands, France or the United Kingdom. Only respondents that gave written informed consent were included in the study. Fast responders (<7 min) who provided nonsensical answers (i.e. gibberish) in open field texts that did not require a response, and duplicates were excluded.

Respondents were recruited via a commercial survey sampling company Survey Engine. In addition to data collection via panels, patients were also recruited via national patient advocacy groups. All respondents received financial compensation upon completion of the questionnaire (£0.50 - £5). The exact amount depended on the channel and country of recruitment. In the Netherlands, data was collected in the first two weeks of August 2020. In the UK and France, data was collected between September and November 2020. The study was approved by the Medical Ethical Testing Committee of the Erasmus Medical Centre (MEC-2019-0248).

2.5. Statistical analyses

The choices respondents made in the DCE were used to assess which trade-offs patients were willing to make regarding mode of administration (implant, pills or injections) and other treatment characteristics. The data from the Netherlands, France and the United Kingdom were pooled, and a country-specific dummy variable was included in the analyses to assess potential differences in preferences between countries.

A main-effects multinomial logit model (MNL) was used as a starting point for model specification. We tested for linearity and higher order polynomials to determine the optimal model specification. To capture heterogeneity in patients’ preferences, a panel latent class multinomial logit model was used. This panel type of model accounts for the multitude of choices each respondent made (i.e. 15 choice tasks per respondent) and assumes subgroups of respondents with different preferences between latent classes, but homogeneous preferences within a class. We do not know how many latent (unobservable) classes there are within the population and each class has its own preference (utility function). However, we can group respondents with similar preference utilities within classes. This is based on the observable data collected, i.e. the individual responses to the choice tasks and respondent’s background demographics. The number of latent classes in which to group the respondents can in theory be between one and the number of individuals in the population [40]. To determine optimal number of latent classes, a range of 2–4 classes were tested using likelihood ratio tests and considering class size and interpretability.

The final model (counterbalancing model fit and interpretability)

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1 Patients were asked about current and past treatment course, choosing among the following 12 therapies: injectables (intramuscular interferon beta (INFβ) 1× per week, subcutaneous (s.c.) INFβ 3× per week, s.c. INFβ once every 2 weeks, s.c. INFβ every 2 days, or glatiramer acetate), oral (dimethyl fumarate, cladribine, teriflunomide, or fingolimod), or infusion therapy (alemtuzumab, natalizumab, ocrelizumab).

2 Due to a technical error, respondents in the UK did not see all questions regarding their current and past treatment course. Some respondents were successfully recontacted about this (n = 72). Respondents who could not be recontacted were resampled (n = 180).

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**Table 1** Attributes and levels of the discrete choice tasks.

| Attribute                  | Attribute Level                                      |
|----------------------------|------------------------------------------------------|
| Risk of relapse            | - 30% less risk                                      |
|                            | - 50% less risk                                      |
|                            | - 70% less risk                                      |
| Reducing disease progression| - 20% less disease progression                       |
|                            | - 40% less disease progression                       |
|                            | - 60% less disease progression                       |
| Risk of side effects       | - Very common mild side effects (more than 10% risk) |
|                            | - Common moderate side effects (1 to 10% risk)       |
|                            | - Rare severe side effects (0.1 to 1% risk)          |
| Mode of administration     | - Injecting treatment once a week                     |
|                            | - Injecting treatment 3 times per week               |
|                            | - Taking 1 pill per day orally                       |
|                            | - Taking 2 pills per day orally                      |
|                            | - Replacing the implant once a year                  |
|                            | - Replacing the implant every 3 years                |

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**Journal of the Neurological Sciences 428 (2021) 117587**
which trade-offs respondents were willing to make to get treatment via what the relative importance of attributes were, and what uptake is used to examine which trade-offs respondents were willing to make, (level) has a positive or negative effect on utility. These coefficients were MS treatment. The sign of the coefficient reflects whether the attribute relative importance of attributes and their levels. For the coefficients, analyses were performed using Apollo software version 0.1.0 [41, 42].

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To walk without aid (yes/no), currently using injections (yes/no). The additional, to provide insight into the likelihood of respondents belonging to a particular latent class of preferences, twelve patient characteristics were included as covariates one-by-one in a so-called class assignment model: country (France/UK/the Netherlands), male (yes/no), higher educated (yes/no), partner (yes/no), RRMS (yes/no), ability to walk with an aid (yes/no), currently using injections (yes/no), and very common mild side effects; implant: replaced once per three years by the coefficients of reduction in risk of relapse and reduction in disease progression, respectively. Secondly, the relative importance of attributes was assessed by taking the difference between the most and least desirable attribute level in each attribute, and dividing this by the sum of differences of all attributes [43]. The larger this value, the larger the relative importance of an attribute. Thirdly, to compare desirability of different modes of administration, mean uptake was predicted for a set of four realistic alternative scenarios; three treatment options (for injections: administered once per week, risk of relapse = 30%, reduce disease progression = 40% and very common mild side effects; implant: replaced once per three years, risk of relapse = 30%, reducing disease progression = 40% and very common mild side effects) and one opt-out (no treatment, unknown risk of relapse, no reduction in disease progression and no side effects). These scenarios were chosen to best reflect the efficacy and safety profile of INF-β (for the injections and implant) and oral therapy. Uptake was predicted by taking the exponent of the utility for the treatment scenario under evaluation divided by the sum of the treatment utility’s exponent and the no treatment utility’s exponent. Uptake was predicted for each class, and for the full sample by weighing the class probabilities.

3. Results

3.1. Respondents

In total 753 respondents (the Netherlands n = 250/1560, France n = 256/5124, the United Kingdom n = 254/4518) met the inclusion criteria, provided informed consent, and completed the questionnaire (response rate: 7% (760/11202)). Data collection ended as soon as the target of 250 respondents per country was reached (10 weeks in the

| Table 2: Patient characteristics. | Total (n = 753) | The Netherlands (n = 250) | France (n = 251) | The United Kingdom (n = 252) | P-value |
|---------------------------------|---------------|--------------------------|----------------|----------------------------|---------|
| Age, mean (SD) | 42 (12.1) | 43.3 (12.2) | 39.2 (11.1) | 43.6 (12.6) | <0.001^2 |
| Female, n (%) | 512 (67.9) | 191 (76.4) | 156 (62.2) | 165 (65.5) | 0.002^3 |
| MS type | | | | | |
| CIS | 39 (5.2) | 6 (2.4) | 25 (9.9) | 8 (3.2) | <0.001^3 |
| RRMS | 404 (53.7) | 149 (59.6) | 124 (49.4) | 131 (51.9) |
| PPMS | 160 (21.3) | 36 (14.4) | 55 (21.9) | 69 (27.4) |
| SPMS | 92 (12.2) | 27 (10.8) | 26 (10.4) | 39 (15.5) |
| Unable to walk | 58 (7.7) | 32 (12.8) | 21 (8.4) | 5 (1.9) |
| Mobility status | | | | | |
| Walk with an aid | 386 (51.3) | 159 (63.6) | 118 (47.0) | 109 (43.3) |
| Walk without aid | 335 (44.5) | 83 (33.2) | 128 (51.0) | 124 (49.2) |
| Treatment course | | | | | |
| Taking 1st-line injectable DMT | 142 (26.4) | 31 (19.5) | 74 (34.6) | 37 (22.3) |
| Not taking 1st-line injectable DMT | 397 (73.7) | 128 (80.5) | 140 (65.4) | 129 (77.7) |
| Marital Status, n (%) | | | | | |
| Unmarried | 164 (21.8) | 58 (23.2) | 62 (24.7) | 44 (17.5) |
| Married | 427 (56.7) | 130 (52.0) | 126 (50.2) | 171 (67.9) |
| Divorced | 50 (6.6) | 20 (8.0) | 16 (6.4) | 14 (5.6) |
| Widowed | 7 (0.9) | 1 (0.4) | 3 (1.2) | 3 (1.2) |
| Education | | | | | |
| Primary education | 19 (2.5) | 3 (1.2) | 8 (3.2) | 8 (3.2) |
| Secondary education | 169 (22.4) | 64 (25.6) | 38 (15.1) | 67 (26.6) |
| Vocational/technical education | 201 (26.7) | 86 (34.4) | 56 (22.3) | 59 (23.4) |
| Other | 307 (40.6) | 102 (40.6) | 45 (17.8) | 72 (28.4) |
| IQ VAS, mean (SD) | 60.56 (20.3) | 61.65 (20.3) | 59.04 (21.7) | 61 (18.9) | 0.09^2 |

SD: standard deviation, CIS: clinically isolated syndrome, RRMS: relapsing-remitting multiple sclerosis, PPMS: primary progressive multiple sclerosis, SPMS: secondary progressive multiple sclerosis, DMT: disease modifying therapy, EQ VAS: EuroQol visual analogue scale. 1Due to a technical error, some respondents in the UK could not answer all questions regarding their current DMT. Some respondents were successfully recontacted about this (n = 72). Respondents who could not be recontacted were resampled (n = 180), 2ANOVA, 3Chi-2 test, 4Fisher’s exact test.

was a two-class model, with two linear and two categorical attribute levels and two alternative specific constants to correct for the order in which the alternatives were presented (left-right bias) and treatment opt-out. The detailed utility function can be found in Appendix B. In addition, to provide insight into the likelihood of respondents belonging to a particular latent class of preferences, twelve patient characteristics were included as covariates one-by-one in a so-called class assignment model. Covariates were only included in the final model if they significantly contributed to the class assignment model (p < 0.05). We tested the contribution of the following categorical parameters to the class assignment model: country (France/UK/the Netherlands), male (yes/no), higher educated (yes/no), partner (yes/no), RRMS (yes/no), ability to walk without aid (yes/no), currently using injections (yes/no). The following continuous variables were dichotomized based on median split: age (≥45), long disease duration (≥ 10 years), high health utility (≥ 0.7), high EQ VAS (≥ 70), good health literacy (≥ 3 score), good numeracy (≥ 4 subjective score + objective scores correct). The final utility function of the class assignment model included relapsing-remitting MS, walking without aid, currently using injections, and country of residence and can also be found in Appendix B. The choice analyses were performed using Apollo software version 0.1.0 [41,42].

The analyses resulted in parameter estimates (β) that indicate the relative importance of attributes and their levels. For the coefficients, the statistical significance (p < 0.05) indicated that respondents considered the attribute important in making their choices concerning MS treatment. The sign of the coefficient reflects whether the attribute (level) has a positive or negative effect on utility. These coefficients were used to examine which trade-offs respondents were willing to make, what the relative importance of attributes were, and what uptake is predicted for various modes of administration. Firstly, to illustrate which trade-offs respondents were willing to make to get treatment via an implant the maximum acceptable risk (MAR) was calculated. This was done by dividing the coefficient of implant replacement every three years by the coefficients of reduction in risk of relapse and reduction in disease progression, respectively. Secondly, the relative importance of attributes was assessed by taking the difference between the most and least desirable attribute level in each attribute, and dividing this by the sum of differences of all attributes [43]. The larger this value, the larger the relative importance of an attribute.

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Netherlands, 6 weeks in the UK, 5 weeks in France). Respondents were excluded if they completed the questionnaire in less than 7 min and provided non-sensical answers (i.e. gibberish) in open questions that did not require a response. Duplicate responses were also excluded. These criteria led to the exclusion of five respondents in the French data (of which two duplicates), two in the English data (one non-sensical speeder and one duplicate) and none of the Dutch respondents.

The characteristics of the patients are displayed in Table 2. The respondents had a mean age of 42 years, 68% were female, over half of the patients had RRMS (54%) and were able to walk without an aid (51%). There are somewhat less female respondents from France and the United Kingdom that completed the survey than you would expect to find in the French and UK MS population (we found 62% and 65.5% female respondents compared to country averages of 71% and 73% in France and the United Kingdom [23,24]). Furthermore, the patients in all three countries had somewhat more progressive disease than you would expect to find in the MS population [22–24], with an average of only 54% having RRMS. The vast majority were currently not taking a first-line injectable DMT. Significant differences were found between the countries for the abovementioned characteristics. Due to using different tariffs the mean health utility significantly differed between the countries and ranged from 0.48 in the United Kingdom, 0.63 in the Netherlands and 0.74 in France, though no significant differences were found in the EQ-VAS (mean score: 60.6).

Respondents generally found the survey easy (strongly agree: 47%) and one-third could have answered more questions (strongly agree: 35%). Most could easily choose between the hypothetical treatments presented to them (35% strongly agreed, 30% somewhat agreed). Three-quarters of respondents somewhat or fully understood the choices between the treatment options from the start of the survey (76%). More detailed results regarding the perception of the survey and the COVID-19 pandemic can be found in Appendix C (Table A1).

### 3.2. Discrete choice experiment

The optimal number of latent classes was two, with class probabilities of 76% for class 1 and 24% in class 2 (Table 3). All attributes in both classes, except the risk of side effects, had statistically significant estimates ($p < 0.05$). In both classes, the negative constant for Treatment 1 indicates that respondents were less likely to choose the treatment alternative presented first as compared to the alternative that followed (i.e. right-left bias).

Patients in class 1 had a statistically significant negative coefficient for the alternative specific constant of no treatment, indicating that they generally preferred any treatment over no treatment, all else being equal. They preferred their treatment to provide less risk of relapse and less disease progression. Rare severe side effects were less desirable than very common mild side effects. Common moderate side effects were perceived not statistically different from very common mild side effects ($p = 0.427$). As compared to the reference level of three injections per week, one pill per day was most preferred followed by an implant once a year and replacing it once every three years were relatively similar.

Patients in class 2, the smaller class, generally preferred no treatment. A lower risk of relapse and reducing disease progression was preferred and rare severe side effects were less desirable than very

### Table 3

Latent class results.

| Class 1 | Coeff. | Std.err. | P-value | Class 2 | Coeff. | Std.err. | P-value |
|---------|--------|----------|---------|---------|--------|----------|---------|
| Constant (no treatment) | −0.405 | 0.110 | <0.001 | Constant (Treatment 1) | 1.818 | 0.195 | <0.001 |
| Constant (Treatment 1) | −0.118 | 0.027 | <0.001 | Reducing risk of relapse | −0.206 | 0.063 | <0.001 |
| Reducing risk of relapse | 0.018 | 0.001 | <0.001 | Reducing disease progression | 0.007 | 0.002 | 0.001 |
| Reducing disease progression | 0.028 | 0.001 | <0.001 | Risk of side effects | 0.012 | 0.003 | 0.000 |
| Very common mild side effects (Ref) | 0.000 | – | – | Very common mild side effects (Ref) | 0.000 | – | – |
| Common moderate side effects | 0.008 | 0.044 | 0.427 | Common moderate side effects | 0.008 | 0.035 | 0.169 |
| Rare severe side effects | −0.116 | 0.042 | 0.003 | Rare severe side effects | −0.170 | 0.087 | 0.025 |
| Mode of administration | | | | | | | |
| Injections 3x per week (Ref) | 0.000 | – | – | Injections 3x per week (Ref) | 0.000 | – | – |
| Injections 1x per week | 0.319 | 0.064 | <0.001 | Injections 1x per week | 0.118 | 0.027 | <0.001 |
| Implant 1x per year | 0.483 | 0.057 | <0.001 | Implant 1x per year | −0.036 | 0.125 | 0.396 |
| Implant 1x per 3 years | 0.481 | 0.061 | <0.001 | Implant 1x per 3 years | 0.513 | 0.124 | <0.001 |
| Pills 2x per day | 0.365 | 0.062 | <0.001 | Pills 2x per day | 0.521 | 0.127 | <0.001 |
| Pills 1x per day | 0.672 | 0.061 | <0.001 | Pills 1x per day | 0.741 | 0.124 | <0.001 |
| Class probability model | | | | | | | |
| Constant | 0.866 | 0.213 | <0.001 | Constant | – | – | – |
| Relapsing-remitting MS (yes) | 0.525 | 0.187 | 0.003 | Relapsing-remitting MS (yes) | – | – | – |
| Mobility (walk without an aid) | −0.382 | 0.191 | 0.023 | Mobility (walk without an aid) | – | – | – |
| Current DMT (injections) | 0.572 | 0.212 | 0.004 | Current DMT (injections) | – | – | – |
| Country (France) | −0.099 | 0.228 | 0.332 | Country (France) | – | – | – |
| Country (The United Kingdom) | 0.263 | 0.232 | 0.128 | Country (The United Kingdom) | – | – | – |
| Average class probability (%) | 76 | | | log-likelihood | 24 | | |
| Akaike Information Criterion (AIC) | 19,038.95 | | | Bayesian Information Criterion (BIC) | 19,244.36 | | |

Coeff. Coefficient. Std.err.: Standard error. Ref: Reference level. MS: multiple sclerosis. DMT: disease modifying treatment.
common mild side effects. Patients in this class were also indifferent between common moderate side effects and very common mild side effects ($p = 0.169$). In this class the order of preference for mode and frequency of administration was like in class 1. However, the coefficient of pills twice per day was slightly higher than the coefficients for implants, whereas injections once per week were not statistically different from the reference level injections three times per week ($p = 0.396$). Again, the coefficients of both frequencies of replacing the implant were relatively close, as was the coefficient of pills twice a day.

As shown by the class size, people were more likely to be in class 1. More specifically, patients with RRMS and who administered medication via injections had a higher probability to belong to this class. Patients who could walk without an aid were more likely to be in class 2 (i.e. negative coefficient in class 1 of class probability model). The country of residence was not statistically significantly related with class membership, indicating little differences in preference structure across countries that was not captured by any of the other covariates included in the class assignment model.

### 3.3. Maximum acceptable risk, relative importance and predicted uptake

The maximum acceptable risk for respondents in class 1 was a 27% increase in risk of relapse to get their treatment via an implant that is replaced once per 3 years rather than injections 3 times per week, all else equal. In class 2, this maximum acceptable risk was 65%. In terms of disease progression, again all else equal, respondents in class 1 were willing to accept 17% disease progression to get their treatment via an implant (replacement once per 3 years), rather than injections 3 times per week. In class 2, this was 39%.

Relative to the other attributes, reducing disease progression was the most important attribute in class 1, while risk of side effects was the least important attribute (Fig. 2). In class 2, mode of administration was the most important attribute, while side effects were least important.

The mean predicted uptake was on average highest for the implant (43%), followed by pills (26%), and injections (21%) when comparing the different modes of administration and their accompanying treatment characteristics (Table 4). Eleven percent of the full sample would not choose any treatment. When comparing uptake of modes of administration, almost half (47%) reported yes, 19% said no, and 34% reported maybe being interested. Frequently mentioned reasons why persons would choose the implant are because it prevents them from having to inject themselves, persons forget to take their treatment, problems with taking oral therapy and ease of use. But before choosing such a device, respondents also mention that they would need to know about the efficacy and safety profile and need more information. Others are hesitant to have an implant in their body and the idea of needing an operation to do so. Furthermore, respondents also mention that they are content with their current treatment and find no need for the implant.

### 4. Discussion

This study aimed to quantify the preferences and trade-offs MS patients were willing to make for three modes of treatment administration (implant, pills and injections) and focussed on whether a novel implantable mode of administration may be accepted by patients given the treatment landscape. Two different preference structures were found that mostly varied in whether respondents would choose the treatments described to them (class 1, which had the largest probability) or not (class 2). As expected, in both classes patients preferred their treatment to reduce risk of relapse and disease progression, and the presence of rare severe side effects had a negative effect on treatment choice as compared to very common mild side effects. Reducing disease progression was the most important treatment characteristic in class 1, while mode of administration was most important for the group hesitant to take treatment. Risk of side effects was least important in both classes. Preferences for modes of administration differed per class, but it was observed that patients generally would be open to having an implant as a mode of administration. Patients were willing to accept an increase in risk of relapse and some disease progression to get their treatment via an implant rather than via injections. Furthermore, the mean predicted uptake was the highest for the implant, followed by pills, injections, and no treatment.

To our knowledge this is the first DCE performed examining an implant as an alternative mode of treatment administration for MS patients. However, research has been conducted in another neurological area. A DCE studying treatment preferences for device-aided modes of

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**Table 4**

| Mode and frequency of administration | Scenario | Average | Class 1 | Class 2 |
|-------------------------------------|----------|---------|---------|---------|
| Implant 1x per 3 years               | 30% less risk of relapse, 40% less disease progression, Very common mild side effects | 43% | 47% | 30% |
| Pills 2x per day                     | 50% risk of relapse, 40% less disease progression, Very common mild side effects | 26% | 27% | 20% |
| Injections 1x per week               | 30% less risk of relapse, 40% less disease progression, Very common mild side effects | 21% | 23% | 12% |
| No treatment (opt-out)               | Unknown risk of relapse, No reduction in disease progression, No side effects | 11% | 2% | 38% |

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*5 27% $= \beta$ (mode of administration: implant 1x per 3 years) *481, all other calculations of maximum acceptable risk were calculated in the same manner.
administration in Parkinson’s Disease in the United States found that patients preferred a medicine pump over deep brain stimulation and oral treatment. Furthermore, the results showed that treatment outcomes such as efficacy and side-effects drove treatment choice, rather than the mode of administration [44]. Our study provides first insights into patient preferences regarding implantable modes of treatment administration in MS, but future research in other (neurological) fields where drug delivery is provided via an implantable device (for example diabetes or spasticity [45,46]) is warranted.

We found that the implant was the most desirable mode of administration (regardless of class allocation) with a mean predicted uptake of 43% for the whole population. Lynd et al. found that factors affecting uptake of a new DMT are efficacy and safety. Patients with MS would switch from an injectable to an oral therapy only if the DMT was at least as effective and safe as an injectable. Though, persons would not switch DMT for convenience reasons if that meant sacrificing efficacy or safety [47]. In contrast, we found that patients would be willing to sacrifice some efficacy to switch from an injectable to implant. Although we found no significant differences in preference structure depending on health literacy and numeracy, we should be aware that understanding benefits and risks of treatment is difficult, and MS patients show poor objective risk-understanding and underestimate risks such as side effects [6], which may explain why patients would sacrifice efficacy or safety. Nevertheless, patients mentioned that more information on efficacy and safety was needed before choosing an implant. Also, physicians, rightly so, may not encourage persons to switch to a less efficacious DMT because of the impact of relapses and progression on the quality of life of patients. Physicians should evaluate patient preferences and shared decision-making is important when deciding on the most appropriate DMT for the patient [48]. Overall, our results suggested that the implant may fit quite nicely into the current mode of treatment administration landscape and persons with MS would be willing to choose this alternative when presented to them.

Our result of patients preferring efficacious treatment and oral therapy over injectable DMTs is in line with previous research examining the preferences of MS patients [7]. In both classes we found that rare severe side effects were significantly less preferred than mild common side effects, and patients were indifferent between mild and moderate side effects. However, regardless of class allocation the safety profile (side effects) was the least important attribute relative to the other attributes. This contrasts to what is usually reported [49–51]. As mentioned above, one should take into account the complexity of interpreting risks as a possible explanation for the fact that the safety profile was deemed to be the safety profile as the least important attribute.

We found differences in preferences according to current DMT (taking a first-line injectable DMT yes or no, where ‘no’ contained persons on oral or IV therapy). A multi-country DCE study performed by Bauer et al. stratified MS patient preferences by current DMT. They found that treatment preferences differed depending on current mode of administration. Among persons currently on injectable DMT, the mode and frequency of administration was significantly less important compared to those currently on IV therapy or oral therapy [52], similar to our results. Furthermore, they found that the safety profile was generally the second the most important attribute to patients regardless of mode of administration, dissimilar to our results. Additionally, persons not currently on injectable DMTs, with progressive forms of MS, and who are mobile are more likely to choose no treatment (class 2). Persons in class 2 find it important to reduce risk of relapse and disease progression, however, we can imagine that these persons have had some (extensive) treatment experience in the past and therefore, now, no longer prefer to have treatment. In a focus group study among Dutch persons with (progressive) MS, negative treatment experiences such as adverse events and doubts about efficacy were reasons why they were currently no longer DMTs [27], and this may hold for the respondents of the DCE also.

For the further development of the Optogenetry implant, it is advised to extend the research with follow-up sessions with MS patients and involve them in the development and validate mock-ups of the device by using these results as a starting point. Also, patient preference information should be incorporated in future health technology appraisals because that information can help guide whether a new technology should be approved for an entire population or only for certain patient subgroups for which there are notable positive health outcomes [10,12].

Our study has several strengths. To our knowledge, we were the first to examine the potential uptake of an implantable mode of treatment administration for MS patients. We followed good research practices and therefore performed a literature search and used qualitative methods, such as focus groups, for the attribute and level development. While this is advised [5], it is not always done [7]. In the focus groups we did a preliminary examination of the views towards treatment preferences and the implantable device, and this DCE has validated those results found. Furthermore, respondents from three different countries were included in the study so the results are a good starting point to examine implantable preferences in other countries and compare those results to ours.

This study has some limitations. Firstly, patients were recruited via online panels and patient advocacy groups in three Western countries. As such, the MS diagnosis was self-reported and only respondents with access to the internet were recruited. Also, although patients are generally more engaged in DCEs compared to the general public [53], response rate was low. These factors may potentially lead to information and selection bias and limited generalizability to other countries. Secondly, though we followed good research practices we did not consult with UK-based MS specialists due to practical constraints. As a consequence, the scope of DMTs that we included might be limited, because the NHS treatment pathway includes infusion therapies as a first-line treatment for highly active RRMS [54]. Additionally, due to practical issues, the pre-test was based on four Dutch MS patients and we did not pre-test in France or the United Kingdom. Furthermore, the priors were based on the pilot performed in the Netherlands and those were set equal for all three countries to enhance comparability of the survey results. However, the respondents from countries differed in some background characteristics. As such, it is possible that patients in different countries responded differently. However, we found no differences in preference structures by country of residence, suggesting the validity of the DCE is intact and therefore we do not think these choices had a great effect on the outcomes. Finally, we examined the preferences and uptake with efficacy and safety profiles most similar to first-line injectable therapies, however most of our patients were taking other treatments, thus perhaps not reflecting their true needs. Nevertheless, patients still preferred the implant, and perhaps this mode may be even more preferred if the efficacy rates are more similar to infusion therapy or second-line treatment (for example, 50%–70% less risk of relapse or 40%–60% less disease progression and potentially more risk of side effects). Future preference studies including the treatment profiles of DMTs such as infusion therapies are needed to make a more comprehensive comparison to the entire treatment landscape.

5. Conclusion

The novel implantable drug delivery device may potentially be an addition to the treatment landscape for persons with MS, and to our knowledge, this was the first stated preference study to examine this possibility. Patients preferred efficacious treatment over side effects. Patients are willing to sacrifice some treatment efficacy to switch from injectable treatment to the implant, though this should be interpreted cautiously because it is difficult for persons to understand the benefit-risk trade-off. Preferences differed per type of MS, current DMT, and mobility. Collecting patient preference information at a timely manner and at multiple phases of medical technology development is important.
to align the needs of the patient to the technology. Further research is needed to examine the position of the implant compared to infusion therapy.

**Funding**

The author(s) disclosed receipt of the following financial support for the research of this article: This work was supported by the European Union’s Horizon 2020 research and innovation program [grant number 720694]. The supporting source had no involvement or restrictions regarding publication.

**Research ethics**

The study was approved by the Medical Ethical Testing Committee of the Erasmus Medical Centre (MEC-2019-0248).

**Consent to participate**

Written informed consent was obtained from all individual participants included in the study.

**Consent for publication**

Patients signed informed consent regarding publishing their data.

**Availability of data and material**

The data that support findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

**Authorship**

Contribution to concept and design of the work: L.A.V, S.P.I-H.; contribution to acquisition, analysis and interpretation of data: L.A.V, S.P.I-H, C.A.UdG., E.W.dBG, W.K.R.; drafted the article: L.A.V, S.P.I-H; revised the draft critically: C.A.UdG, E.W.dBG, W.K.R.; approved version of manuscript to be published: L.A.V, S.P.I-H, C.A.UdG., E.W.dBG, W.K.R.; each author participated sufficiently in the work to take public responsibility for appropriate portions of the context: L.A.V, S.P.I-H, C.A.UdG., E.W.dBG, W.K.R.

**Declaration of Competing Interest**

None.

**Acknowledgements**

We acknowledge grants from the European Union’s Horizon 2020 research and innovation program [grant number 720694].

**Appendix A. Description of the attributes and levels presented to the respondents**

**Part 2: Questions about treatment characteristics**

In the next part of the survey you will be presented with 8 choices on MS treatments. We are interested to know which of the treatments you would prefer. There are no right or wrong answers. You will be asked to make a choice between the different treatment options presented. The treatment options may seem very similar, but the little differences make that it is important for us that you answer all the questions carefully and completely. Below you will find an explanation on four characteristics relating to the MS treatments in this study. Please read this carefully. Afterwards you will get some example questions.

**Risk of relapse:** Multiple sclerosis is a disease characterized by relapses (also known as an exacerbation or a flare-up). An MS treatment may reduce the risk of a relapse. The risk of a relapse, in comparison to no treatment, differs per treatment and may have the following values, such as:

- 30% less risk of getting a relapse (in comparison to no treatment)
- 50% less risk of getting a relapse (in comparison to no treatment)
- 70% less risk of getting a relapse (in comparison to no treatment)

**Reducing disease progression:** Multiple sclerosis is a disease that causes damage to the brain and spinal cord. The nerves become damaged and are less capable of transmitting signals to and from the brain. Consequently, you may suffer from nerve damage. Reducing the risk of disease progression (also known as worsening), in comparison to no treatment, differs per treatment and may have the following values, such as:

- 20% less disease progression (in comparison to no treatment)
- 40% less disease progression (in comparison to no treatment)
- 60% less disease progression (in comparison to no treatment)
Mode of administration: MS treatments can be administered in different ways. In this study we will examine three different modes of administration: injecting the treatment, taking the treatment orally via a pill, and receiving the treatment via an implant.

You may take the pill any moment of the day orally. The frequency of administering the pill differs per treatment option.

The injectable treatments are provided via a pre-filled syringe. The frequency of administering the injection differs per treatment option.

The implant is a medical device (6cm x 2cm x 0.2cm; imagine a thin USB stick). The implant is placed by the surgeon at the outpatient clinic and is implanted underneath the skin in the lower back (see image). The implant releases the MS treatment, with the correct dosage, into your body. You do not have to administer the treatment yourself, meaning no injections or pills are needed. The implant will be replaced every so often.

The mode and frequency of administration differ per treatment and may have the following values, such as:
- Injecting treatment 1 time per week
- Injecting treatment 3 times per week
- Taking 1 pill per day orally
- Taking 2 pills per day orally
- Replacing the implant 1 time per year
- Replacing the implant 1 time every 3 years

Risk of side effects: MS treatment may be associated with a risk of developing mild and severe side effects. The risk of developing side effects differs per treatment option.

Very commonly occurring mild side effects are flu-like symptoms, gastro-intestinal symptoms and injection-site reactions (occur in more than 10% of all patients).

Commonly occurring moderate side effects are headache, fatigue, dizziness, and urinary tract or respiratory infections (occur in 1 to 10% of all patients).

Rarely occurring, severe (possibly life threatening) side effects are an infection of the brain (progressive multifocal leukoencephalopathy), liver toxicity and post-operative wound infection (occur in 0.1 to 1% of all patients).

The risk of developing the side effects differ per treatment option and can have the following values, such as:
- Very common mild side effects (more than 10% risk)
- Common moderate side effects (1 to 10% risk)
- Rare severe side effects (0.1 to 1% risk)

Appendix B. Utility functions

The utility function was specified as follows:

\[
V_{\text{nsj}}(treatment) = \beta_0(treatment) + \beta_1(treatment) \text{ reduction risk of relapse} + \beta_2(treatment) \text{ reduction of disease progression} + \beta_3(treatment) \text{ risk of side effects, common moderate nsj} + \beta_4(treatment) \text{ risk of side effects, rare severe nsj} + \beta_5(treatment) \text{ mode of administration, injections 1x per week nsj} + \beta_6(treatment) \text{ mode of administration, implant 1x per year nsj} + \beta_7(treatment) \text{ mode of administration, implant 1x per 3 years nsj} + \beta_8(treatment) \text{ mode of administration, pills 2x per day nsj} + \beta_9(treatment) \text{ mode of administration, pills 1x per day nsj}.
\]

\[
V_{\text{optout}}(treatment) = \beta_{10},
\]

where \(V_{\text{nsj}}\) is the observed utility of participant \(n\) in class \(c\) for choice set \(s\) for alternative \(j\). The constant \(\beta_{10}\) and \(\beta_{10c}\) represent the alternative specific constants for respectively the alternative that was presented first, and last (i.e. the opt-out). \(\beta_1\) to \(\beta_9\) indicate the class-specific parameter weights (or coefficients) of each attribute level. Reference levels are not included in the utility function and can be found in Table 3.

The final class assignment utility function was:
\[ V_{\text{rel}} = \beta_0 + \beta_1 \text{MS} + \beta_2 \text{injections} + \beta_3 \text{France} + \beta_4 \text{United Kingdom}. \]

### Appendix C. Concluding questions and influence of COVID-19

Table A1: Concluding questions and the influence of the COVID-19 pandemic on responses.

| Conclusion Questions                                   | Total Population | The Netherlands | France | The United Kingdom |
|--------------------------------------------------------|------------------|-----------------|--------|-------------------|
|                                                        | Frequency | Percent | Frequency | Percent | Frequency | Percent | Frequency | Percent |               |
| The survey was easy:                                   |           |         |           |         |           |         |           |         |               |
| Strongly agree                                         | 355       | 47.1    | 87        | 34.5    | 144       | 57.4    | 124       | 49.6    |
| Somewhat agree                                         | 178       | 23.6    | 73        | 28.9    | 49        | 19.5    | 56        | 22.4    |
| Neutral                                                | 141       | 18.7    | 64        | 25.4    | 28        | 11.2    | 49        | 19.6    |
| Somewhat disagree                                      | 77        | 10.2    | 27        | 10.7    | 30        | 12.0    | 20        | 8.0     |
| Strongly disagree                                      | 2         | 0.3     | 1         | 0.4     | 1         | 0.4     | 1         | 0.4     |
| I could have answered more questions:                  |           |         |           |         |           |         |           |         |               |
| Strongly agree                                         | 262       | 34.8    | 61        | 24.2    | 97        | 38.7    | 104       | 41.6    |
| Somewhat agree                                         | 169       | 22.4    | 72        | 28.6    | 54        | 21.5    | 43        | 17.2    |
| Neutral                                                | 183       | 24.3    | 60        | 23.8    | 54        | 21.5    | 69        | 27.6    |
| Somewhat disagree                                      | 95        | 12.6    | 47        | 18.7    | 28        | 11.2    | 20        | 8.0     |
| Strongly disagree                                      | 44        | 5.8     | 12        | 4.8     | 18        | 7.2     | 14        | 5.6     |
| I could easily choose between the treatments:          |           |         |           |         |           |         |           |         |               |
| Strongly agree                                         | 268       | 35.6    | 55        | 21.8    | 115       | 45.8    | 98        | 39.2    |
| Somewhat agree                                         | 228       | 30.3    | 90        | 35.7    | 58        | 23.1    | 80        | 32.0    |
| Neutral                                                | 151       | 20.1    | 78        | 31.0    | 38        | 15.1    | 35        | 14.0    |
| Somewhat disagree                                      | 78        | 10.4    | 24        | 9.5     | 29        | 11.6    | 25        | 10.0    |
| Strongly disagree                                      | 28        | 3.7     | 5         | 2       | 11        | 4.4     | 14        | 4.8     |
| I fully understood the choices from the beginning:     |           |         |           |         |           |         |           |         |               |
| Strongly agree                                         | 404       | 53.7    | 95        | 37.7    | 129       | 51.4    | 180       | 72.0    |
| Somewhat agree                                         | 169       | 22.4    | 75        | 29.8    | 55        | 21.9    | 39        | 15.6    |
| Neutral                                                | 92        | 12.2    | 38        | 15.1    | 34        | 13.6    | 20        | 8.0     |
| Somewhat disagree                                      | 71        | 9.4     | 39        | 15.5    | 25        | 10.7    | 7         | 2.8     |
| Strongly disagree                                      | 17        | 2.2     | 5         | 2       | 8         | 3.2     | 4         | 1.6     |
| I found some of the presented treatments difficult to imagine: |           |         |           |         |           |         |           |         |               |
| Strongly agree                                         | 141       | 18.7    | 32        | 12.7    | 66        | 26.3    | 43        | 17.2    |
| Somewhat agree                                         | 198       | 26.3    | 45        | 17.9    | 74        | 29.5    | 79        | 31.6    |
| Neutral                                                | 178       | 23.6    | 72        | 28.6    | 51        | 20.3    | 55        | 22.0    |
| Somewhat disagree                                      | 145       | 19.3    | 75        | 29.8    | 39        | 15.5    | 31        | 12.4    |
| Strongly disagree                                      | 91        | 12.1    | 28        | 11.1    | 21        | 8.4     | 42        | 16.8    |
| I found all treatment characteristics were equally important: |           |         |           |         |           |         |           |         |               |
| Strongly agree                                         | 227       | 30.2    | 51        | 20.2    | 108       | 43.0    | 68        | 27.2    |
| Somewhat agree                                         | 211       | 28.0    | 79        | 31.4    | 71        | 28.3    | 61        | 24.4    |
| Neutral                                                | 164       | 21.8    | 72        | 28.6    | 41        | 16.3    | 51        | 20.4    |
| Somewhat disagree                                      | 121       | 16.1    | 41        | 16.3    | 26        | 10.4    | 54        | 21.6    |
| Strongly disagree                                      | 50        | 6.4     | 9         | 3.6     | 5         | 2       | 16        | 6.4     |

**COVID-19 questions**

Do you think that the current situation with regards to the coronavirus has influenced your answers during the questionnaire?

- No influence: 336 (44.6%)
- Some influence: 148 (19.7%)
- Moderate influence: 138 (18.3%)
- Severe influence: 95 (12.6%)
- Extreme influence: 36 (4.8%)

*Are you/ have you been infected with the coronavirus?*

- No, I have been tested and had a negative result: 204 (27.1%)
- Probably not, but I haven’t been tested: 446 (59.2%)
- Probably yes, but I haven’t been tested: 71 (9.4%)
- Yes, I have been tested and had a positive test result: 32 (4.3%)

*I am at risk of being infected with the coronavirus*

- No risk: 33 (4.4%)
- Low risk: 204 (27.1%)
- Somewhat at risk: 298 (39.6%)
- High risk: 159 (21.1%)
- Extremely high risk: 59 (7.8%)

*I am at risk of getting sick once infected with the coronavirus*

- No risk: 26 (3.5%)
- Low risk: 102 (13.6%)
- Somewhat at risk: 270 (35.9%)
- High risk: 251 (33.3%)
- Extremely high risk: 104 (13.8%)

*I am at risk of dying once infected with the coronavirus*

- No risk: 48 (6.4%)
- Low risk: 221 (29.4%)

(continued on next page)
### Table A1 (continued)

| Frequency | Percent | Frequency | Percent | Frequency | Percent | Frequency | Percent |
|-----------|---------|-----------|---------|-----------|---------|-----------|---------|
| Somewhat at risk | 252 | 33.5 | 89 | 35.3 | 83 | 33.1 | 80 | 32.0 |
| High risk | 153 | 20.3 | 60 | 23.8 | 57 | 22.7 | 36 | 14.4 |
| Extremely high risk | 79 | 10.5 | 27 | 10.7 | 39 | 15.5 | 13 | 5.2 |

Are you concerned becoming infected with the coronavirus?

- I am not concerned: 45, 6.0, 8, 3.2, 14, 5.6, 23, 9.2
- I have little concern: 118, 15.7, 24, 9.5, 39, 15.5, 55, 22.0
- I have some concern: 278, 36.9, 100, 39.7, 65, 25.9, 113, 45.2
- I have many concerns: 213, 28.3, 84, 33.3, 81, 32.3, 48, 19.2
- I am extremely concerned: 99, 13.2, 36, 14.3, 52, 20.7, 11, 4.4

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