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The impact of reproductive issues on preferences of women with relapsing multiple sclerosis for disease modifying treatments

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Abstract

Background: Relapsing-remitting multiple sclerosis (RRMS) is an incurable disease characterised by relapses (periods of function loss) followed by full or partial recovery, and

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potential permanent disability over time. Many disease modifying treatments (DMTs) exist which help reduce relapses and slow disease progression. Most are contraindicated during conception/pregnancy, and some require a discontinuation period before trying to conceive. Although around three-quarters of people with RRMS are women, there is limited knowledge about how reproductive issues impact DMT preference.

Aim: To measure the preferences for DMTs of women with RRMS who are considering pregnancy.

Design: An online discrete choice experiment (DCE).

Methods: Participants chose between two hypothetical DMTs characterised by a set of attributes, then they indicated if they preferred their choice to no treatment. Attributes were identified from interviews and focus groups with people with RRMS and MS professionals, and literature reviews, and included probability of problems with pregnancy, discontinuation of DMTs, and breastfeeding safety. In each DCE task participants were asked to imagine making decisions in three scenarios: now; when trying to conceive; and when pregnant.

Analysis: Two mixed logit models were estimated, one to assess the statistical significance between scenarios and one in maximum acceptable risk space to allow comparison of the magnitudes of parameters between scenarios.

Sample: Women with RRMS who were considering having a child in future, recruited from a UK MS patient Register.

Results: *N*=60 respondents completed the survey. Participants preferred no treatment in 12.6% of choices in the now scenario, rising significantly to 37.6% in the trying-to-conceive and 60.3% in the pregnant scenarios (Kruskal-Wallis $p<.001$). This pattern corresponds with results from models, which included a no treatment alternative specific constant (ASC) capturing

differences between taking and not taking a DMT not specified by the attributes. The ASC was lower in the trying to conceive than in the now scenario and lower still in the pregnant scenario, indicating an intrinsic preference for no treatment. Participants also placed relatively less preference on reducing relapses and avoiding disease progression in the trying-to-conceive and pregnant scenarios compared to a lower risk of problems with pregnancy. In the trying-to-conceive scenario, participants' preference for treatments with shorter washout periods increased.

Conclusion: Women with RRMS considering having a child prefer DMTs with more favourable reproduction related attributes, even when not trying to conceive. Reproductive issues also influence preferences for DMT attributes not directly related to pregnancy, with preferences dependent on the life circumstances in which choices were made. The DCE's design highlights the benefits of considering the scenario in which participants make choices, as they may change over time.

Key points

- We used a discrete choice experiment (DCE) to study the preferences for disease modifying treatments (DMTs) of women with relapsing-remitting multiple sclerosis who may consider having a child
- Using an innovative design we elicited preferences in three scenarios: now, when trying to conceive, and when pregnant.
- In the trying-to-conceive and pregnant scenarios, participants were more likely to choose no treatment, with participants having both a greater intrinsic preference for no treatment and also considering the benefits of treatment relatively less important compared to potential problems with pregnancy.

1. Introduction

Multiple sclerosis (MS) is an incurable inflammatory and degenerative disease of the central nervous system [1-3] which affects an estimated 150 people in every 100,000 [4]. Around 75% of people with MS are women [5] and the disease typically first appears in younger people, with the mean age of diagnosis at around 30 years. [6, 7]. The most common form of the disease at diagnosis is relapsing-remitting multiple sclerosis (RRMS), which affects around 85% of patients [1]. RRMS is characterised by temporary episodes of loss of function termed relapses, followed by full or partial recovery, with a wide range of symptoms including loss of vision, mobility problems, pain, fatigue and cognitive impairment [1].

No cure exists for MS, but there are many disease modifying treatments (DMTs) available for RRMS which can reduce the frequency of relapses and lower the risk of accumulating disability [8, 9]. Individuals' choices as to which DMT to take, or whether to take a DMT at all, can be complex, as treatments vary in efficacy and side effect profile. They also vary in mode of administration, with tablet, self-injection and infusion based treatments all available [10, 11].

Reproductive choices have an impact on the decision of which (if any) DMT to take (and vice versa). [12-14]. Although some DMTs (e.g. glatiramer acetate) are safe to be taken in pregnancy [15] others are contraindicated due to problems with conception, pregnancy and/or breastfeeding and there is a lack of evidence for some DMTs as to whether they are safe during conception/pregnancy or not [16-20]. Risks associated with some DMTs include increased risks of miscarriage, premature birth, low birth weight and congenital anomalies. Further complicating the decision-making context is the fact that pregnancy and childbirth can affect the course of women's MS. For example, some evidence suggests women may experience a reduction in their relapse-rate when pregnant, but an increased risk of relapse in the post-partum period [21-24], though more recent evidence does not support the hypothesis of an increase in disease activity post-partum [25] Finally, there is evidence that some women with RRMS have concerns about the impact of their disease on their ability to care for a new-born [26, 27], which

has the potential to influence preferences for treatment. Yet, the influence of reproductive issues on women's preferences is still not well understood. Clinician advice around reproduction and DMTs may vary due to the lack of an evidence-base on treatment safety particularly for newer treatments [28-31]. A better understanding of how reproduction influences women's preferences for DMTs could help to develop more effective strategies to support their decision making process.

This study uses a discrete choice experiment (DCE) to investigate the impact reproductive issues have on women's DMT preferences [32-34]. It is part of a wider project entitled Considering RIsk and benefits in Multiple Sclerosis treatment selection (CRIMSON), which examined people with RRMS' preferences for and attitudes towards DMTs using a variety of approaches. The project included qualitative studies [35], literature reviews [12, 34] and two linked DCEs, one without reproduction related attributes, and the current study which specifically examined reproduction. The evidence from these studies was then used in the development of a patient decision aid [36] for people with RRMS making DMT choices [37].

Previous DCE studies have explored people's preferences for MS treatments [34, 38-40], but only one has explored how reproductive issues impact treatment preferences [41], and reproduction has been highlighted as a neglected area in the DCE literature in MS [34].

This study's primary aim was to examine reproduction related attributes of DMTs in detail. We recruited women considering having a child in future, for whom reproductive issues were assumed to be most relevant [12]. The study also aimed to capture the dynamic nature of DMT decision-making, and how reproduction influences choices at different points in people's lives. Participants were asked to imagine making their choices between DMTs in three different scenarios: now, when trying to conceive, and when pregnant. An additional aim of the study

was to assess the feasibility of using such a design, and whether participants would make systematically different choices in different scenarios.

2. Methods

Sample

The target population was women with RRMS (wwRRMS) who indicated they intended to have children in future. Recruitment was done online using the MS Register (ukmsregister.org), a large UK panel of people with MS who are regularly invited to participate in research surveys. The MS Register has over 15,000 people registered, although only a fraction had consented to receive invitations from third parties to take part in research such as this study at the time of recruitment. No payment is given for participation.

Materials

In line with good practice [42, 43], the survey instrument was developed using a qualitative process and following established guidelines [44-46]. This involved interviews (N=30) with people with RRMS [35] and three focus groups (N=17) with people with RRMS, neurologists and MS nurses to generate candidate attributes.

A finding which emerged from the qualitative data collection was that reproduction-related aspects of DMTs were important factors in many participants' decision-making. Reproductive issues were also identified as a neglected topic in DCEs in MS [12, 34]. However, including reproduction-specific attributes in a DCE targeted at all people with RRMS would not give an appropriate measure of their importance, since they would only be relevant to a subset of the target population. The original study design of a single DCE was hence changed in response to the emerging qualitative findings. This resulted in two DCEs, one without reproduction-

specific attributes with a target population of all people with RRMS, and one with wwRRMS who were considering having a child in the future.

A ranking exercise was conducted with four workshops (*N*=33) with people with RRMS to prioritise which attributes to include. In order not to overburden participants, two attributes included in the general DCE were excluded from the reproduction DCE. Participants were asked to assume that all DMTs in the reproduction DCE were identical in terms of the two attributes from the main DCE which were dropped.[14] A draft survey was refined in an iterative process of 28 think-aloud interviews with people with RRMS. This process addressed whether the survey was understandable, whether attributes and levels were interpreted as intended, whether the tasks presented an acceptable burden, and general presentation and usability issues. Probabilistic risk information was presented using simple numerical formats accompanied by visual aids (see Figure 1), following evidence-based principles to facilitate understanding [47, 48]. The final list of attributes and levels for the reproduction DCE is given in Table 1, and the attributes and levels included only in the general DCE are given in the supplementary online material, as well as a copy of the survey which shows how attributes and levels were explained to participants.

The reproduction DCE had a dual response, multiple scenario design. Participants first chose which of two DMTs they preferred, and then indicated whether they preferred it to no treatment. They were also asked to imagine making decisions in three scenarios. First they were asked to imagine making their choice now, then making their choice when trying to conceive, and

[14] The two attributes were relapse severity and chance of additional long-term and/or life-threatening medical condition over 4 years.

finally making their choice when pregnant. Figure 1 gives screenshots of a sample question, and Figure 2 shows how each individual sub-question was presented sequentially.

A Bayesian D-efficient statistical design for the reproduction DCE was created using Ngene[15] with a main effects model with zero priors. Choices where one treatment was superior on all levels apart from mode of administration were excluded. The final design had 10 blocks of five questions each. The NGene code is available as online supplementary material. The order attributes were presented in was randomised between participants, but consistent across questions for a given participant, and pregnancy specific attributes were grouped together.

Procedure

Participants completed a DCE without reproduction related attributes, then a short series of questions about themselves, their RRMS and treatment history. Both male and female participants were asked "Are you or your partner thinking about having a child, either soon or in the next few years? (yes/no)." If they responded yes, they were asked to complete the reproduction DCE. Male participants completed a reproduction DCE without the attribute Safe to breastfeed or the pregnant choice scenario. These data were not analysed due to a small sample size (N=7). Participants were asked if they were currently trying to conceive or currently pregnant, with the aim of incorporating this information into the modelling (see below).

Analysis

[15]ChoiceMetrics

The fraction of times each participant chose no treatment as their most preferred option in each scenario was calculated. The statistical significance of differences between scenarios was assessed using a Kruskal-Wallis test.

The utility individual i receives from choosing treatment j over the alternative treatment in choice situation k was assumed to take the form

$$u_{ijk} = \beta_{ik} x_{ijk} + \varepsilon_{ijk}.$$

Here x_{ijk} is a vector indicating the levels of each attribute for treatment j in situation k, β_{ik} is a vector describing i's preferences and ε_{ijk} is an independent and identically distributed extreme valued error term. The utility that i receives from choosing no treatment over treatment is assumed to take the same form as the above equation, with the addition of an alternative specific constant (ASC). The 'no treatment' ASC is interpreted as capturing all aspects of taking no treatment compared to taking a DMT not explicitly captured by the attributes. For example, it might include an intrinsic desire for treatment due to being on a DMT giving a sense of control over an individual's disease, over and above any benefits it brings [12]. Alternatively, it might include an intrinsic preference for avoiding treatment to prevent it affecting an unborn child, over and above any explicitly stated risk.

The probability of choosing treatment $j \in \{1,2\}$ over treatment $l \neq j$ in the first stage and then preferring $n \epsilon \{j, no\ treatment\}$ in the second stage is

$$P(j,n) = \left(\frac{e^{V_j}}{e^{V_j} + e^{V_l}}\right)\left(\frac{e^{V_n}}{e^{V_j} + e^{V_{notreatment}}}\right)$$

where $V_j = \beta_{ik} x_{ijk}$ is the deterministic component of utility.

A mixed logit model was used, with coefficients, including the no treatment ASC, assumed to be normally distributed, i.e. for coefficient m, $\beta_{imk}\ N(\mu_{mk}, \sigma_m^2)$. Both normally and log-

normally distributed parameters are common assumptions [49]. The former was chosen as normal distributions allow the possibility of a parameter having no influence of average preferences, which was considered a plausible possibility. The influence of scenarios is captured by letting

$$\mu_{mk} = \left(\mu_m^{now} + \mu_m^{conceive} t_k^{conceive} + \mu_m^{pregnant} t_k^{pregnant}\right)$$

where the dummy variables $t_k^{conceive}$ and $t_k^{pregnant}$ take the value 1 either if choice situation k is in the trying-to-conceive/pregnant scenario or if i indicated she was currently trying to conceive/pregnant and take the value 0 otherwise. The term μ_m^{now} gives the parameter mean in the now scenario, and the terms $\mu_m^{conceive}$ and $\mu_m^{pregnant}$ show how the parameter mean changes in the trying-to-conceive and pregnant scenarios. The standard deviation of parameters is assumed to be the same in all scenarios. For participants who reported they were trying to conceive/pregnant, preferences were assumed to be identical in the conceive/pregnant scenario and the now scenario.

The model above was designed to maximise the chances of seeing if differences in preferences across scenarios were statistically significant. However, comparing the magnitudes of model parameters in different scenarios may result in problems, as changes may be due to a shift in response scale rather than different preferences [50]. The influence of the response scale can be eliminated by choosing one parameter as a numeraire, and the magnitude of other parameters compared to it. Here, problems with pregnancy[16] was chosen as the numeraire, so that other

[16] Participants were told that risks could include low birth weight, premature birth or miscarriage, with the levels of risk presented to participants of similar magnitude to those observed in the literature [51, 52].

attributes were expressed in terms of the maximum acceptable risk (MAR) of problems with pregnancy.

Two models were estimated. One was designed to assess whether differences between scenarios were statistically significant, and the other was designed to allow comparison of the magnitudes of participants' preferences between scenarios. The utility to person i of choosing treatment j in choice situation k was modelled as

$$u_{ijk} = \boldsymbol{\alpha}_{ik}\boldsymbol{x}_{ijk} + \lambda_i r_{jk} + \eta_{ijk}$$

where r_{jk} is the risk of problems with pregnancy for j, λ_i represents i's preferences for risk of problems with pregnancy, $\boldsymbol{\alpha}_{ik}$ is a vector representing her preferences for other attributes and η_{ijk} is an error term. This may be rearranged to give

$$u_{ijk} = \lambda_i\left(\boldsymbol{\gamma}_{ik}\boldsymbol{x}_{ijk} + r_k\right) + \eta_{ijk}$$

where $\boldsymbol{\gamma}_{ik} = {}^{\boldsymbol{\alpha}_{ik}}/_{\lambda_i}$ gives i's MAR of problems with pregnancy to receive an extra unit of other attributes. This formulation is analogous to models estimated in willingness-to-pay space [53, 54] and has the advantage that a distribution can be directly assumed for MAR. Calculating MAR from the results of the previous model would require taking the ratio of two normal distributions, which has undefined moments.

The influence of different scenarios was captured by letting $\boldsymbol{\gamma}_{ik} = \sum_s \boldsymbol{\gamma}_i^s t_k^s$, $s\epsilon\{now, conceive, pregnant\}$, so in contrast to the previous model, coefficients in the conceive and pregnant scenarios were not interaction terms. The parameter λ_i was modelled as following a log-normal distribution and the γ_i^s's were modelled as following normal distributions. Means were allowed to vary over scenarios (with the exception of λ_i to ensure the model was identified) but variances were not, as it was not possible to robustly estimate a model without this restriction.

Models were estimated using the Apollo choice modelling package for R [55]. Statistical significance of model coefficients was assessed using *t*-tests and was judged at the 5% level.

3. Results

Invitations to take part were sent to approximately 1,500 people. A total of 675 out of 845 (80%) participants completing the survey reported being female. Of these, 61 indicated they (or their partner) were considering having a child, either in the present or future. A total of 60 completed the reproduction DCE. Of these, 14 were currently trying to conceive, and nobody reported currently being pregnant. Table 2 summarises participants' demographics and their experiences with DMTs.

Most participants had been living with MS for some years (median four years) and almost 90% had experience of taking a DMT at some point. As few participants were treatment naïve, the DCE tasks of choosing between DMTs were relevant to them. Around a quarter of participants reported having a child/children in their household, so many will also have had previous experience of pregnancy.

In the now scenario, no treatment was chosen 12.6% of the time, which rose to 37.6% in the trying to conceive scenario and 60.3% in the pregnant scenario.[17] A Kruskal-Wallis test confirmed the differences across scenarios were statistically significant ($p<.001$).

The results of model estimation are given in Table 3. In the now scenario, participants were significantly more likely to choose treatments giving fewer relapses, a lower probability of progression and without severe side effects. Daily pills were the most preferred mode of administration, although the difference in preference between two infusions a year apart and a

[17] Participants who were currently trying to conceive making choices in the now scenario were modelled as being in the trying to conceive scenario.

daily pill was not significant. Injection and monthly infusions were significantly less popular than pills. Participants preferred treatments with a lower chance of problems with pregnancy. Although the sign of the parameter means indicate that participants preferred treatments with shorter washout times (i.e. with a shorter time to leave their system once they stop treatment) and which were safe to breastfeed on, neither was statistically significant. They were also significantly more likely to choose treatments with a lower chance of problems with pregnancy and which were safe to breastfeed on. The mean no treatment ASC (which captured preferences for taking no treatment not explicitly captured by the attributes) was negative, indicating a preference for taking a DMT over and above their properties captured by the attributes, but not significant.

The coefficients for the trying-to-conceive and pregnant scenarios are interaction terms, and represent changes in preferences relative to the now scenario. There were seven significant interactions for the trying-to-conceive scenario. For number of relapses, probability of progression, moderate and severe side effects, injection and monthly infusions, the interactions reduced the absolute magnitude of the parameter, indicating a lesser importance in decision-making. The interaction for washout period increased the absolute magnitude of the parameter, indicating greater importance in decision-making compared to the now scenario (Table 3).

There were six significant interactions in the pregnant scenario. Five reduced the absolute magnitude of the parameter, meaning lower importance in decision-making: number of relapses, chance of progression, moderate and severe side effects, and monthly infusions. The interaction for the no treatment ASC was positive, and sufficiently large to increase the absolute magnitude of the parameter. This implies that the differences between no treatment and treatment not explicitly captured by the attributes had greater importance in decision-making compared to the now scenario, and that in the pregnant scenario participants preferred no treatment.

Table 4 gives the results of the model in maximum acceptable risk (MAR) space. To aid comparison between scenarios, the results are illustrated in Figure 3. Unlike Table 3, the figure shows absolute preferences for the trying-to-conceive and pregnant scenarios, not changes relative to the now scenario, and preferences in different scenarios may be compared as they are measured in terms of MAR of problems with pregnancy. MAR of problems with pregnancy was lower in the trying-to-conceive and pregnant scenarios than in the now scenario for reducing the number of relapses, lowering the chance of progression, and avoiding moderate and severe side effects. There was also lower MAR of problems with pregnancy to obtain a daily pill rather than an injection or a monthly infusion. There was little difference in MAR for the above attributes between the trying-to-conceive and pregnant scenarios. MAR was similar across scenarios for a shorter washout period and having a treatment which is safe to breastfeed on. The greatest changes across scenarios were seen for the no treatment ASC. Participants had a MAR of problems with pregnancy of 33.7% in the now scenario, which reduced to 19.0% in the trying to conceive scenario and -14.7% in the pregnant scenario, the negative sign implying a preference for no treatment over treatment.

4. Discussion

Considering the now scenario and the non-pregnancy-related attributes, results are as expected, and in line with previous DCE findings (e.g. [39, 40]). Participants were more likely to choose treatments which reduced the number of relapses experienced, and the probability of future loss of function, and with less severe side effects. As has previously been observed [56-59], participants preferred a daily pill over other modes of administration. The daily pill may fit better into participants' daily lives, despite its increased frequency compared to other modes of administration. This notion is in accordance with findings from the qualitative data gathered during attribute development suggesting that pills were easier to incorporate into a normal routine, for example taking them alongside vitamins [60]. The similarities between previous

studies which recruited from the population of all people with RRMS and this study which elicited the views of wwRRMS considering pregnancy suggests there are few fundamental differences between the two populations in attitudes towards non-pregnancy-specific attributes of DMTs.

In the now scenario, even when not actively trying to conceive, risk of problems with pregnancy influenced participants' choices. Two possible explanations of this finding, are: first, participants may have recognised the possibility of an unplanned pregnancy, given that the rate of unplanned pregnancies has been estimated to be as high as 50% [61], leading them to choose pregnancy-friendly treatments in case of this eventuality. Corroboration for this was found in the qualitative attribute development work, where some interview participants identified unplanned pregnancy as a worry about taking DMTs [35, 60]. Alternatively, participants may have wished to avoid the disruption associated with switching or stopping treatment and choose a DMT now that they would be happy to continue taking when trying to conceive or pregnant. Both explanations have the underlying rationale of the safety of a potential foetus, and are not mutually exclusive.

Participants' preferences varied according to scenario type. There was a dramatic increase in the number of times no treatment was the most preferred option, from just over 10% in the now scenario, to just under 40% when trying to conceive, to around 60% when pregnant. A large driver of this change was interactions with the no treatment ASC, which had the largest relative magnitude in both the trying-to-conceive and pregnant scenarios. The ASC captured general preferences for no treatment over any DMT not captured by preferences for the attributes, and so the interactions can be interpreted as participants being more reluctant to take any sort of treatment while pregnant, irrespective of the particular properties of the treatment. The above results are in line with previous findings that many women cease taking DMTs when trying to conceive or pregnant, with the aim of resuming treatment at some point after childbirth.

The shift in preferences towards no treatment was also driven by relatively lower importance of non-reproduction specific attributes of treatments. In both the trying-to-conceive and pregnant scenarios, number of relapses, chance of future progression, side effect severity and having a preferred mode of administration became relatively less important. This may indicate that when participants began actively trying to conceive, they would change the trade-offs they would make between their own current/future health and risks to a foetus. It also suggests that participants were more willing in those scenarios to take treatments which are less convenient and more disruptive to their lifestyle as long as they experience a safer pregnancy. However, these trade-offs appear to be stable between the trying-to-conceive and pregnant scenarios.

In Table 3 the interactions for chance of problems with pregnancy were insignificant in both the trying to conceive and pregnant scenarios. However, Figure 3 reveals that what individuals considered an acceptable risk of problems with pregnancy for beneficial attributes of treatments changes across scenarios, in line with the patterns discussed above.

The term problems with pregnancy encompasses several conditions with varying severity, such as low birth weight and congenital abnormalities. Different participants may hence have had different perceptions of how severe problems may be. A single attribute was used partly to ensure the number of attributes was not so large as to overburden participants, and partly as in pre-testing, participants showed an aversion to terms such as congenital abnormalities. Future research could elicit more details about preferences and trade-offs between specific risks of DMTs.

Participants had similar relative preferences for different modes of administration across all scenarios. Yet Figure 3 shows that the maximum acceptable risks (MARs) of problems with pregnancy were reduced by similar amounts in the trying-to-conceive and pregnant scenarios. This may suggest that participants were more willing in those scenarios to take treatments

which are less convenient and more disruptive to their lifestyle as long as they experience a safer pregnancy.

The results for the washout period can also be interpreted in line with a behavioural pattern of not wanting to take a DMT when pregnant: Participants were most likely to choose treatments with shorter washout periods in the trying-to-conceive scenario, which could indicate that if they were willing to take a DMT in this period, they would place a premium on being able to stop as soon as possible when they become pregnant.

This study has some innovative features. It was the first stated preference study to examine reproduction-related attributes of DMTs in detail. It was also the first to focus on wwRRMS who may consider having a child, the population for whom reproductive issues are most pertinent.

Another innovative feature of the study is that it reflected the dynamic nature of DMT decision-making, especially when considering pregnancy, by asking participants to imagine completing the DCE tasks in multiple scenarios. The feasibility of such a design has been demonstrated here: results were logical, and in line with expectations and previous results. Participants responded to the different scenarios, changing their behaviour both in regard to the relative importance of DMT attributes and whether to take a DMT or not.

This study also has limitations. Scenarios were presented in the same order in each task (i.e., now, trying to conceive, pregnant). This design was chosen based on pre-testing, which found difficulties in communicating the concept of the task to participants. Presenting the scenarios in their logical order was important to make the tasks understandable to participants. However, this set order implies that order effects may have affected results to some extent. Future methodological work could usefully investigate the trade-offs between avoiding possible order

effects by randomising the order of scenarios and the increased complexity of the tasks for participants.

Choices in the trying-to-conceive and pregnant scenarios were (for the majority of participants) being made for the future. There is a large body of evidence that individuals' preferences can be time-inconsistent [58-60], and that individuals are generally poor at predicting what their experiences of future health states will be [61]. The current study measures people's intentions as to what they will choose in the future, which may not correspond to their actual decisions when the time comes. While this is not necessarily a limitation in itself, as studying individuals' intentions is still important and relevant, there may be a gap between intention and action.

The sample size was small, although many DCEs have smaller sample sizes (e.g. [62]). Relatively few questions were asked due to the necessity of minimising respondent burden after already having answered several DCE questions. This means that there may be significant differences across scenarios which the DCE does not have sufficient power to detect.

Another drawback to the low sample size was that it was difficult to explore heterogeneity. People were invited to complete the DCE if they reported that they were "considering having a child, either now or in the next few years". Respondents who answered yes may have had various underlying reasons for doing so, ranging from currently trying to conceive to a general aspiration to have a child at some point in the future. The choice situations may hence have had differing relevance for participants. Although mixed logit models were used to account for heterogeneity, it is difficult to know why preferences differed across respondents. Future research could usefully explore potential sources of preference heterogeneity such as previous experience of pregnancy, disease severity, or when an individual is planning to have a child in future.

The small sample size indicates that the population of wwRRMS who are considering pregnancy is both relatively small and/or relatively difficult to engage. This does not imply, however, that issues relating to reproduction and DMTs are unimportant. Newly diagnosed wwRRMS are typically in their 20s, and the number for whom reproduction-related attributes of DMTs are relevant at any given time-point is lower than the number for whom they were/will be important at some point in their lives. Women who have not yet received an RRMS diagnosis, who have children and do not wish for more, who are no longer able to have children, or whose disease has become progressive, may not have found the DCE tasks meaningful to complete. Yet each group would find them meaningful at some time.

Another weakness of this study was that it was performed as an addition to another DCE. A consequence of this is that although, in line with best practice [42, 43], qualitative methods were used to develop the survey instrument, some qualitative participants were not part of the target population of this DCE. It is also not possible to know how many were part of the target population, since the inclusion criteria for the DCE emerged relatively late in the study. On the other hand, that the relationship between reproduction and DMTs was an important, complex and time-sensitive topic to investigate was only revealed due to the extensive qualitative process used to develop the survey instrument, which could be regarded as a strength of the research project. In addition, as attributes and levels draw upon a large amount of qualitative data, there is a greater certainty than in many MS stated preference studies [34] that they were relevant to participants, were understandable, and were interpreted by participants as researchers intended.

The sample was self-selected from an online panel used to regularly completing surveys related to their disease, and may not be representative of the wider population of wwRRMS who were considering having a child in future. In addition, it is a limitation that some participants may not have found the reproduction attributes included relevant if, e.g., they were planning to adopt.

There is opportunity for further work in this area. For example, future studies could explore heterogeneity of preferences, as decisions around reproduction are extremely personal. It would be instructive to investigate whether wwRRMS who are not currently considering having a child in future also consider reproduction-related factors in DMT decision-making. Given the difficulties of recruiting wwRRMS who were considering having a child, future studies could consider eliciting the preferences of wwRRMS who have previously had children. One drawback of that approach is that their preferences may be affected by recall bias [63]. Future studies may wish to study the preferences for men as well as women. Reproduction-related issues affect men's DMT choices as well [64], and it is difficult to know to what extent the findings for women would be replicated with men. However, this project highlighted challenges to recruiting sufficient numbers of men.

More generally, this study has demonstrated that reproduction-specific attributes of non-reproduction treatments can have great importance to individuals. Many treatments for conditions other than RRMS, such as anti-depressants, seizure medication and steroids, can have risks for a foetus if taken during pregnancy [7, 65]. However, the impact of reproduction-related risks of treatments is often neglected in the DCE literature. Some research has been carried out into preferences for reproduction-specific treatments such as in vitro fertilisation [66-68], obstetric care [69], perinatal depression [70], and smoking cessation during pregnancy [71]. However, these do not involve trade-offs between treatment benefits and reproduction risks. Several studies on prenatal testing [72-75] elicit trade-offs between beneficial aspects of tests and risks to the foetus. Future DCEs looking at preferences for treatments with reproduction-related risks may wish to use an approach similar to the current study to examine the importance of such risks in patients' decision-making.

5. Conclusion

The results of this study indicate that wwRRMS considering having a child in future have preferences for reproduction-related attributes of DMTs, even when not actively trying to conceive. They also indicate that DMT decision-making in relation to reproduction is complex, and depends heavily on context. The findings from this study and the wider research project have been used as evidence to inform the content and structure of a patient decision aid for people making decisions about starting, switching and stopping taking DMTs for RRMS [37]. This study demonstrates that using multiple scenarios in a DCE is feasible and understandable by survey participants, and can improve the insight a study gives into complex decision-making situations in which participants' preferences may change over time. Future DCEs may wish to consider adopting a similar approach.

Compliance with ethical standards

Informed consent

All participants gave informed consent before completing the survey, as well as consent to merge their responses with data from the UK MS Register.

Ethics approval

Approval for this study was given by an NHS Research Ethics Committee.

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Data availability statement

Data is not publically available as consent was not obtained for this from participants, However, data may be shared on a case by case basis if a formal data sharing agreement is entered into by contacting either the corresponding author or Leeds Institute of Health Sciences.

Contributions

All authors conceived the study, defined the study aims and contributed to survey design. EW and DM collected data. EW conducted statistical analysis and wrote the manuscript first draft. All authors contributed to and approved the final manuscript.

Conflict of interest

JC has received support from the Efficacy and Mechanism Evaluation Programme and Health Technology Assessment Programme (NIHR); UK Multiple Sclerosis Society and National Multiple Sclerosis Society; Rosetrees Trust. In the last three years, he has been a local principal investigator for trials in multiple sclerosis funded by Receptos, Novartis and Biogen Idec, and has received an investigator grant from Novartis outside this work. He has taken part in Advisory Boards/consultancy for Roche, Merck, MedDay, Biogen and Celgene.

KS has received consulting fees from Biogen, Merck, Novartis and Roche, and received payments for lecturing activities from Biogen, Merck, Novartis, Roche and Teva.

HB provides guidance based on her academic expertise in medical decision making to health policy organisations, patient advocacy groups, health professionals and health scientists on research methods and techniques to develop and evaluate patient decision aids and shared decision making interventions. Her time and expenses in attending meetings, carrying out evaluations and collaborating with other projects are remunerated. HB does not gain financially from outcomes or outputs of these collaborations.

References

[1] D. S. Reich, C. F. Lucchinetti, and P. A. Calabresi, "Multiple Sclerosis," *New England Journal of Medicine,* vol. 378, pp. 169-180, 2018.

[2] A. J. Thompson, B. L. Banwell, F. Barkhof, W. M. Carroll, T. Coetzee, G. Comi*, et al.*, "Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria," *The Lancet Neurology,* vol. 17, pp. 162-173, 2018.

[3] R. M. Bove and S. L. Hauser, "Diagnosing multiple sclerosis: Art and science," *The Lancet Neurology,* vol. 17, pp. 109-111, 2018.

[4] M. T. Wallin, W. J. Culpepper, E. Nichols, Z. A. Bhutta, T. T. Gebrehiwot, S. I. Hay*, et al.*, "Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016," *The Lancet Neurology,* vol. 18, pp. 269-285, 2019.

[5] E. Kingwell, J. J. Marriott, N. Jetté, T. Pringsheim, N. Makhani, S. A. Morrow*, et al.*, "Incidence and prevalence of multiple sclerosis in Europe: a systematic review," *BMC neurology,* vol. 13, p. 128, 2013.

[6] World Health Organization, "Atlas: multiple sclerosis resources in the world 2008," 2008.

[7] W. J. Brownlee, T. A. Hardy, F. Fazekas, and D. H. Miller, "Diagnosis of multiple sclerosis: progress and challenges," *The Lancet,* vol. 389, pp. 1336-1346.

[8] G. Comi, M. Radaelli, and P. Soelberg Sørensen, "Evolving concepts in the treatment of relapsing multiple sclerosis," *The Lancet,* vol. 389, pp. 1347-1356.

[9] W. Castro-Borrero, D. Graves, T. C. Frohman, A. B. Flores, P. Hardeman, D. Logan*, et al.*, "Current and emerging therapies in multiple sclerosis: a systematic review," *Therapeutic Advances in Neurological Disorders,* vol. 5, pp. 205-220, 2012.

[10] A. Rae-Grant, G. S. Day, R. A. Marrie, A. Rabinstein, B. A. Cree, G. S. Gronseth*, et al.*, "Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology," *Neurology,* vol. 90, pp. 789-800, 2018.

[11] Ø. Torkildsen, K. M. Myhr, and L. Bø, "Disease ‐ modifying treatments for multiple sclerosis – a review of approved medications," *European Journal of Neurology,* vol. 23, pp. 18-27, 2016.

[12] I. Eskyte, A. Manzano, G. Pepper, S. Pavitt, H. Ford, H. Bekker*, et al.*, "Understanding treatment decisions from the perspective of people with relapsing remitting multiple Sclerosis: A critical interpretive synthesis," *Multiple sclerosis and related disorders,* 2018.

[13] P. K. Coyle, "Management of women with multiple sclerosis through pregnancy and after childbirth," *Therapeutic Advances in Neurological Disorders,* vol. 9, pp. 198-210, 2016/05/01 2016.

[14] D. Payne and K. M. McPherson, "Becoming mothers. Multiple sclerosis and motherhood: A qualitative study," *Disability and Rehabilitation,* vol. 32, pp. 629-638, 2010/01/01 2010.

[15] M. Sandberg-Wollheim, O. Neudorfer, A. Grinspan, B. Weinstock-Guttman, J. Haas, G. Izquierdo*, et al.*, "Pregnancy Outcomes from the Branded Glatiramer Acetate Pregnancy Database," *International journal of MS care,* vol. 20, pp. 9-14, Jan-Feb 2018.

[16] E. Lu, B. W. Wang, C. Guimond, A. Synnes, D. Sadovnick, and H. Tremlett, "Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review," *Neurology,* vol. 79, pp. 1130-1135, 2012.

[17] P. K. Coyle, S. Sinclair, A. Scheuerle, J. Thorp, J. Albano, and M. Rametta, "Final results from the Betaseron (interferon β-1b) Pregnancy Registry: a prospective observational study of birth defects and pregnancy-related adverse events," *BMJ open,* vol. 4, p. e004536, 2014.

[18] J. Fares, A. H. Nassar, S. Gebeily, F. Kobeissy, and Y. Fares, "Pregnancy outcomes in Lebanese women with multiple sclerosis (the LeMS study): a prospective multicentre study," *BMJ open,* vol. 6, p. e011210, 2016.

[19] R. Alroughani, A. Altintas, M. Al Jumah, M. Sahraian, I. Alsharoqi, A. AlTahan*, et al.*, "Pregnancy and the use of disease-modifying therapies in patients with multiple sclerosis: benefits versus risks," *Multiple sclerosis international,* vol. 2016, 2016.

[20] R. Dobson, P. Dassan, M. Roberts, G. Giovannoni, C. Nelson-Piercy, and P. A. Brex, "UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines," *Practical Neurology,* vol. 19, pp. 106-114, 2019.

[21] S. E. Hughes, T. Spelman, O. M. Gray, C. Boz, M. Trojano, A. Lugaresi*, et al.*, "Predictors and dynamics of postpartum relapses in women with multiple sclerosis," *Multiple Sclerosis Journal,* vol. 20, pp. 739-746, 2014.

[22] C. Confavreux, M. Hutchinson, M. M. Hours, P. Cortinovis-Tourniaire, T. Moreau, and P. i. M. S. Group, "Rate of pregnancy-related relapse in multiple sclerosis," *New England Journal of Medicine,* vol. 339, pp. 285-291, 1998.

[23] A. L. Phillips, M. K. Houtchens, and N. C. Edwards, "Multiple Sclerosis Relapse Rates, Before, During, and After Pregnancy: a US Retrospective Claims Database Analysis (P1. 361)," ed: AAN Enterprises, 2017.

[24] S. Vukusic and R. Marignier, "Multiple sclerosis and pregnancy in the'treatment era'," *Nature Reviews Neurology,* vol. 11, p. 280, 2015.

[25] A. Langer-Gould, J. B. Smith, K. B. Albers, A. H. Xiang, J. Wu, E. H. Kerezsi*, et al.*, "Pregnancy-related relapses and breastfeeding in a contemporary multiple sclerosis cohort," *Neurology,* vol. 94, pp. e1939-e1949, 2020.

[26] K. I. Pakenham, J. Tilling, and J. Cretchley, "Parenting difficulties and resources: The perspectives of parents with multiple sclerosis and their partners," *Rehabilitation Psychology,* vol. 57, p. 52, 2012.

[27] J. Kosmala-Anderson and L. M. Wallace, "A qualitative study of the childbearing experience of women living with multiple sclerosis," *Disability and Rehabilitation,* vol. 35, pp. 976-981, 2013/06/01 2013.

[28] A. Wundes, R. N. Pebdani, and D. Amtmann, "What do healthcare providers advise women with multiple sclerosis regarding pregnancy?," *Multiple sclerosis international,* vol. 2014, 2014.

[29] N. Borisow, A. Döring, C. F. Pfueller, F. Paul, J. Dörr, and K. Hellwig, "Expert recommendations to personalization of medical approaches in treatment of multiple sclerosis: an overview of family planning and pregnancy," *EPMA Journal,* vol. 3, p. 9, 2012.

[30] N. Borisow, F. Paul, S. Ohlraun, D. Pach, F. Fischer, and J. Dörr, "Pregnancy in multiple sclerosis: a questionnaire study," *PloS one,* vol. 9, p. e99106, 2014.

[31] M. Lee and P. O'brien, "Pregnancy and multiple sclerosis," *Journal of Neurology, Neurosurgery & Psychiatry,* vol. 79, pp. 1308-1311, 2008.

[32] V. Soekhai, E. W. de Bekker-Grob, A. R. Ellis, and C. M. Vass, "Discrete choice experiments in health economics: past, present and future," *PharmacoEconomics,* vol. 37, pp. 201-226, 2019.

[33] M. D. Clark, D. Determann, S. Petrou, D. Moro, and E. W. de Bekker-Grob, "Discrete Choice Experiments in Health Economics: A Review of the Literature," *PharmacoEconomics,* vol. 32, pp. 883-902, 2014.

[34] E. J. Webb, D. Meads, I. Eskyte, N. King, N. Dracup, J. Chataway, *et al.*, "A systematic review of discrete-choice experiments and conjoint analysis studies in people with multiple sclerosis," *The Patient-Patient-Centered Outcomes Research,* vol. 11, pp. 391-402, 2018.

[35] A. Manzano, I. Eskytė, H. L. Ford, H. Bekker, B. Potrata, J. Chataway, *et al.*, "Impact of Communication on First Treatment Decisions in People with Relapsing-Remitting Multiple Sclerosis," *Patient Education & Counseling,* 2020.

[36] K. R. Sepucha, P. Abhyankar, A. S. Hoffman, H. L. Bekker, A. LeBlanc, C. A. Levin, *et al.*, "Standards for UNiversal reporting of patient Decision Aid Evaluation studies: the development of SUNDAE Checklist," *BMJ Qual Saf,* vol. 27, pp. 380-388, 2018.

[37] A. Manzano, H. L. Ford, B. Potrata, I. Eskyte, D. Meads, E. Webb, *et al.*, *Treatment Decision Making and Relapsing Remitting Multiple Sclerosis. The CRIMSON Project Decision Aid Booklet.* . Leeds: University of Leeds, 2019. https://crimson.leeds.ac.uk/wp-content/uploads/sites/51/2019/12/UOL169_CRIMSON-A4-Brochure_WEB.pdf

[38] C. Poulos, E. Kinter, J. van Beek, K. Christensen, and J. Posner, "Preferences of patients with multiple sclerosis for attributes of injectable multiple sclerosis treatments in the United Kingdom and France," *International Journal of Technology Assessment in Health Care,* vol. 34, pp. 425-433, 2018.

[39] C. Bottomley, A. Lloyd, G. Bennett, and N. Adlard, "A discrete choice experiment to determine UK patient preference for attributes of disease modifying treatments in Multiple Sclerosis," *Journal of Medical Economics,* pp. 1-8, 2017.

[40] F. R. Johnson, G. Van Houtven, S. Ozdemir, S. Hass, J. White, G. Francis, *et al.*, "Multiple sclerosis patients' benefit-risk preferences: serious adverse event risks versus treatment efficacy," *Journal of Neurology,* vol. 256, pp. 554-62, Apr 2009.

[41] P. Wicks, D. Brandes, J. Park, D. Liakhovitski, T. Koudinova, and R. Sasane, "Preferred features of oral treatments and predictors of non-adherence: two web-based choice experiments in multiple sclerosis patients," *Interactive Journal of Medical Research,* vol. 4, p. e6, Mar 05 2015.

[42] J. Coast, H. Al‐Janabi, E. J. Sutton, S. A. Horrocks, A. J. Vosper, D. R. Swancutt, *et al.*, "Using qualitative methods for attribute development for discrete choice experiments: issues and recommendations," *Health Economics,* vol. 21, pp. 730-741, 2012.

[43] M. E. Kløjgaard, M. Bech, and R. Søgaard, "Designing a stated choice experiment: the value of a qualitative process," *Journal of Choice Modelling,* vol. 5, pp. 1-18, 2012.

[44] E. M. Janssen, J. B. Segal, and J. F. P. Bridges, "A Framework for Instrument Development of a Choice Experiment: An Application to Type 2 Diabetes," *The Patient - Patient-Centered Outcomes Research,* vol. 9, pp. 465-479, 2016/10/01 2016.

[45] J. F. Bridges, A. B. Hauber, D. Marshall, A. Lloyd, L. A. Prosser, D. A. Regier, *et al.*, "Conjoint analysis applications in health—a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force," *Value in Health,* vol. 14, pp. 403-413, 2011.

[46] I. L. Hollin, B. M. Craig, J. Coast, K. Beusterien, C. Vass, R. DiSantostefano, *et al.*, "Reporting Formative Qualitative Research to Support the Development of Quantitative Preference Study Protocols and Corresponding Survey Instruments: Guidelines for Authors and Reviewers," *The Patient-Patient-Centered Outcomes Research,* vol. 13, pp. 121-136, 2020.

[47] L. J. Trevena, B. J. Zikmund-Fisher, A. Edwards, W. Gaissmaier, M. Galesic, P. K. Han, *et al.*, "Presenting quantitative information about decision outcomes: a risk

communication primer for patient decision aid developers," *BMC medical informatics & decision making,* vol. 13, p. S7, 2013.

[48] D. A. Zipkin, C. A. Umscheid, N. L. Keating, E. Allen, K. Aung, R. Beyth*, et al.*, "Evidence-based risk communication: a systematic review," *Annals of internal medicine,* vol. 161, pp. 270-280, 2014.

[49] E. Lancsar, D. G. Fiebig, and A. R. Hole, "Discrete choice experiments: a guide to model specification, estimation and software," *Pharmacoeconomics,* vol. 35, pp. 697-716, 2017.

[50] S. Hess and J. M. Rose, "Can scale and coefficient heterogeneity be separated in random coefficients models?," *Transportation,* vol. 39, pp. 1225-1239, 2012.

[51] M. Amato, E. Portaccio, A. Ghezzi, B. Hakiki, V. Zipoli, V. Martinelli*, et al.*, "Pregnancy and fetal outcomes after interferon-β exposure in multiple sclerosis," *Neurology,* vol. 75, pp. 1794-1802, 2010.

[52] R. Boskovic, R. Wide, J. Wolpin, D. Bauer, and G. Koren, "The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort," *Neurology,* vol. 65, pp. 807-811, 2005.

[53] K. Train and M. Weeks, "Discrete choice models in preference space and willingness-to-pay space," in *Applications of simulation methods in environmental and resource economics*, ed: Springer, 2005, pp. 1-16.

[54] A. R. Hole and J. R. Kolstad, "Mixed logit estimation of willingness to pay distributions: a comparison of models in preference and WTP space using data from a health-related choice experiment," *Empirical Economics,* vol. 42, pp. 445-469, 2012.

[55] S. Hess and D. Palma, "Apollo: a flexible, powerful and customisable freeware package for choice model estimation and application," *Journal of Choice Modelling,* p. 100170, 2019.

[56] J. M. Garcia-Dominguez, D. Munoz, M. Comellas, I. Gonzalbo, L. Lizan, and C. Polanco Sanchez, "Patient preferences for treatment of multiple sclerosis with disease-modifying therapies: a discrete choice experiment," *Patient preference & adherence,* vol. 10, pp. 1945-1956, 2016.

[57] L. D. Lynd, A. Traboulsee, C. A. Marra, N. Mittmann, C. Evans, K. H. Li*, et al.*, "Quantitative analysis of multiple sclerosis patients' preferences for drug treatment: a best-worst scaling study," *Therapeutic Advances in Neurological Disorders,* vol. 9, pp. 287-96, Jul 2016.

[58] L. S. Wilson, A. Loucks, G. Gipson, L. Zhong, C. Bui, E. Miller*, et al.*, "Patient preferences for attributes of multiple sclerosis disease-modifying therapies: development and results of a ratings-based conjoint analysis," *International Journal of Ms Care,* vol. 17, pp. 74-82, Mar-Apr 2015.

[59] L. Wilson, A. Loucks, C. Bui, G. Gipson, L. Zhong, A. Schwartzburg*, et al.*, "Patient centered decision making: use of conjoint analysis to determine risk-benefit trade-offs for preference sensitive treatment choices," *Journal of the Neurological Sciences,* vol. 344, pp. 80-7, Sep 15 2014.

[60] A. Manzano, H. L. Ford, G. Pepper, J. Chataway, K. Schmierer, D. Meads*, et al.*, "CRIMSON - Considering Risk and benefits In Multiple Sclerosis treatment selectiON," 30, 2019.

[61] S. K. Henshaw, "Unintended pregnancy in the United States," *Family planning perspectives,* pp. 24-46, 1998.

[62] J. Spinks, M. Janda, H. P. Soyer, J. A. Whitty, and telecare, "Consumer preferences for teledermoscopy screening to detect melanoma early," *Journal of telemedicine,* vol. 22, pp. 39-46, 2016.

[63] J. K. Schmier, M. T. Halpern, and o. research, "Patient recall and recall bias of health state and health status," *Expert review of pharmacoeconomics,* vol. 4, pp. 159-163, 2004.

[64] C. Pecori, M. Giannini, E. Portaccio, A. Ghezzi, B. Hakiki, L. Pastò, *et al.*, "Paternal therapy with disease modifying drugs in multiple sclerosis and pregnancy outcomes: a prospective observational multicentric study," *BMC neurology,* vol. 14, p. 114, 2014.

[65] J. R. Hardy, B. P. Leaderer, T. R. Holford, G. C. Hall, and M. B. Bracken, "Safety of medications prescribed before and during early pregnancy in a cohort of 81 975 mothers from the UK General Practice Research Database," *Pharmacoepidemiology and drug safety,* vol. 15, pp. 555-564, 2006.

[66] L. Van Den Wijngaard, M. Van Wely, E. A. Dancet, N. M. Van Mello, C. A. Koks, F. Van Der Veen, *et al.*, "Patients' preferences for gonadotrophin-releasing hormone analogs in in vitro fertilization," *Gynecologic obstetric investigation,* vol. 78, pp. 16-21, 2014.

[67] E. Landfeldt, B. Jablonowska, E. Norlander, K. Persdotter-Eberg, A. Thurin-Kjellberg, M. Wramsby, *et al.*, "Patient preferences for characteristics differentiating ovarian stimulation treatments," *Human reproduction,* vol. 27, pp. 760-769, 2012.

[68] I. W. van Empel, E. A. Dancet, X. H. Koolman, W. L. Nelen, E. A. Stolk, W. Sermeus, *et al.*, "Physicians underestimate the importance of patient-centredness to patients: a discrete choice experiment in fertility care," *Human Reproduction,* vol. 26, pp. 584-593, 2011.

[69] M. Pavlova, M. Hendrix, E. Nouwens, J. Nijhuis, and G. van Merode, "The choice of obstetric care by low-risk pregnant women in the Netherlands: implications for policy and management," *Health Policy,* vol. 93, pp. 27-34, 2009.

[70] J. Ride and E. Lancsar, "Women's preferences for treatment of perinatal depression and anxiety: a discrete choice experiment," *PloS one,* vol. 11, 2016.

[71] H. Morgan, P. Hoddinott, G. Thomson, N. Crossland, S. Farrar, D. Yi, *et al.*, "Benefits of Incentives for Breastfeeding and Smoking cessation in pregnancy (BIBS): a mixed-methods study to inform trial design," *Health Technology Assessment,* vol. 19, 2015.

[72] L. Beulen, J. P. Grutters, B. H. Faas, I. Feenstra, H. Groenewoud, J. M. van Vugt, *et al.*, "Women's and healthcare professionals' preferences for prenatal testing: a discrete choice experiment," *Prenatal diagnosis,* vol. 35, pp. 549-557, 2015.

[73] F. E. Carroll, H. Al‐Janabi, T. Flynn, and A. A. Montgomery, "Women and their partners' preferences for Down's syndrome screening tests: a discrete choice experiment," *Prenatal diagnosis,* vol. 33, pp. 449-456, 2013.

[74] M. Hill, J. Fisher, L. S. Chitty, and S. Morris, "Women's and health professionals' preferences for prenatal tests for Down syndrome: a discrete choice experiment to contrast noninvasive prenatal diagnosis with current invasive tests," *Genetics in medicine,* vol. 14, pp. 905-913, 2012.

[75] Y. M. Chan, D. S. Sahota, T. Y. Leung, K. W. Choy, O. K. Chan, and T. K. Lau, "Chinese women's preferences for prenatal diagnostic procedure and their willingness to trade between procedures," *Prenatal Diagnosis: Published in Affiliation With the International Society for Prenatal Diagnosis,* vol. 29, pp. 1270-1276, 2009.

Table 1: Attributes and levels

Attribute	Level 1	Level 2	Level 3	Level 4	No treatment level
Average number of relapses over 4 years	1 relapse	2 relapses	3 relapses		4 relapses
Average number of people whose functioning is significantly worse after 10 years	650 out of 1000 (65%)	700 out of 1000 (70%)	750 out of 1000 (75%)		800 out of 1000 (80%)
Typical side effects of treatment	Mild – no additional medication	Moderate – manage with over the counter medication	Severe – manage with MS clinic visit		
How you take the treatment	Pill taken daily, takes less than a minute at a convenient location	Self-injection every two days, takes 10-15 mins at a convenient location	Infusion (drip) once a month, takes several hours at a hospital	Two infusion (drip) treatments, 1 year apart, takes several days at a hospital	
Chance of problems with pregnancy if taken during conception/pregnancy	*200 out of 1000 (20%)*	*300 out of 1000 (30%)*	*400 out of 1000 (40%)*		*200 out of 1000 (20%)*
Time for drug to leave your system after stopping treatment	*0 months*	*1 month*	*3 months*		
Safe to breastfeed	*Yes*	*No*			*Yes*

Note. Attributes in italics were specific to the reproduction DCE and not included in the general DCE

Table 2: Demographic characteristics

Variable	N	(%)
Age		
Mean (standard deviation)	34.4	(6.1)
Highest education level obtained		
Secondary school	6	(10)
Occupational qualification	9	(15)
Degree	16	(26.7)
Postgraduate qualification	21	(35)
Other	2	(3.3)
Missing	6	(10)
Occupation		
(Self-)employed	41	(68.3)
Unemployed	4	(6.7)
Voluntary work	1	(1.7)
Housework	2	(3.3)
Not working due to temporary/permanent disability	4	(6.7)
Other	1	(1.7)
Missing	6	(10)
Are children under 18 living in participant's household?	16	(26.7)
Current MS type		
PPMS	2	(3.3)
RRMS	55	(91.7)
SPMS	1	(1.7)
Don't know	2	(3.3)
MS type at diagnosis		
RRMS	59	(98.3)
Don't know	1	(1.7)
Years since MS symptoms first experienced		
Median (range)	5.5	(1-22)
Missing	2	(3.3)
Years since MS diagnosis		
Median (range)	4	(1-22)
Missing	1	1.7
DMT naive	7	(11.7)
Currently taking DMT	47	(78.3)
For non-DMT naive participants, number of DMTs experienced		
Median (range)	2	(1-4)
N	60	

Note. Italics indicate data from MS Register

Table 3: Model estimation results

		Now		Trying to conceive interaction		Pregnant interaction	
		Mean	s.d.	Mean	s.d.	Mean	s.d.
Number of relapses		-1.08*	1.17*	0.877*	0.725	0.919*	0.328
		(0.276)	(0.284)	(0.309)	(0.483)	(0.305)	(0.360)
% chance of progression		-0.207*	0.107*	0.188*	0.231	0.199*	0.0817
		(0.0516)	(0.0521)	(0.0428)	(0.124)	(0.0529)	(0.0650)
Side effects	Mild	Baseline					
	Moderate	-0.981*	1.04*	1.30*	0.439	1.38*	0.414
		(0.391)	(0.412)	(0.561)	(0.604)	(0.513)	(0.533)
	Severe	-1.50*	1.81	1.88*	2.64	1.80*	0.476
		(0.557)	(1.31)	(0.773)	(1.52)	(0.629)	(1.34)
Administration	Pill	Baseline					
	Injection	-1.88*	1.35*	1.84*	1.26	1.38	1.29*
		(0.746)	(0.442)	(0.790)	(0.646)	(0.822)	(0.599)
	Monthly	-1.46*	1.09	2.46*	0.548	1.89*	0.199
	IV	(0.576)	(0.603)	(0.716)	(1.17)	(0.732)	(0.804)
	Yearly IV	-0.817	2.22*	0.914	2.07	0.913	0.31
		(0.632)	(0.551)	(0.689)	(1.13)	(0.688)	(0.901)
Washout period		-0.339	0.588*	-0.793*	0.57	-0.214	0.275
(months)		(0.201)	(0.199)	(0.299)	(0.292)	(0.223)	(0.242)
% chance problems with pregnancy		-0.110*	0.148*	-0.105	0.09	-0.0283	0.123*
		(0.0240)	(0.0462)	(0.0644)	(0.0523)	(0.0324)	(0.0508)
Safe to breastfeed	Yes	Baseline					
	No	-0.71	1.27*	-0.0295	2.02*	0.0261	0.807
		(0.400)	(0.561)	(0.526)	(1.02)	(0.461)	(0.647)
No treatment ASC		-1.15	1.91*	0.332	2.71*	3.74*	5.30*
		(1.07)	(0.885)	(1.31)	(1.01)	(1.20)	(1.05)

Note. Standard errors in parentheses; * indicates significance at the 5% level; s.d. = standard deviation; 900 observations from 60 participants; log-likelihood = -758.81

Table 4: Estimation results of model in maximum acceptable risk space

		Now	Trying to conceive	Pregnant	Standard deviation
Number of relapses		13.1*	2.82*	4.89*	6.30*
		(0.860)	(0.281)	(0.526)	(0.493)
% chance of progression		2.12*	0.408*	0.427*	1.39*
		(0.0627)	(0.0918)	(0.113)	(0.0719)
Side effects	Mild	Baseline			
	Moderate	9.89*	-1.37	2.59*	4.92*
		(0.136)	(0.873)	(0.790)	(1.27)
	Severe	30.4*	14.3*	16.2*	19.4*
		(3.39)	(0.953)	(2.64)	(1.50)
Administration	Pill	Baseline			
	Injection	19.1*	10.2*	10.7*	-0.256
		(3.80)	(1.98)	(1.40)	(0.657)
	Monthly IV	15.4*	1.89	-0.968	11.4*
		(0.167)	(2.65)	(1.28)	(0.100)
	Yearly IV	-1.87	0.732	0.359	11.4*
		(3.02)	(1.96)	(2.07)	(1.00)
Washout period (months)		5.51*	6.53*	6.15*	5.71*
		(0.109)	(0.307)	(0.240)	(0.270)
% chance problems with pregnancy		-0.110*			1.68*
		(0.139)			(0.138)
Safe to breastfeed	Yes	Baseline			
	No	6.69*	7.08*	8.68*	1.16*
		(0.366)	(0.701)	(2.32)	(0.222)
No treatment ASC		35.7*	19.0*	-14.7*	29.5*
		(4.15)	(2.04)	(0.203)	(2.19)

Note. Standard errors in parentheses; * indicates significance at the 5% level; s.d. = standard deviation; 900 observations from 60 participants; log-likelihood = -744.78

Figure 1: Example choice task

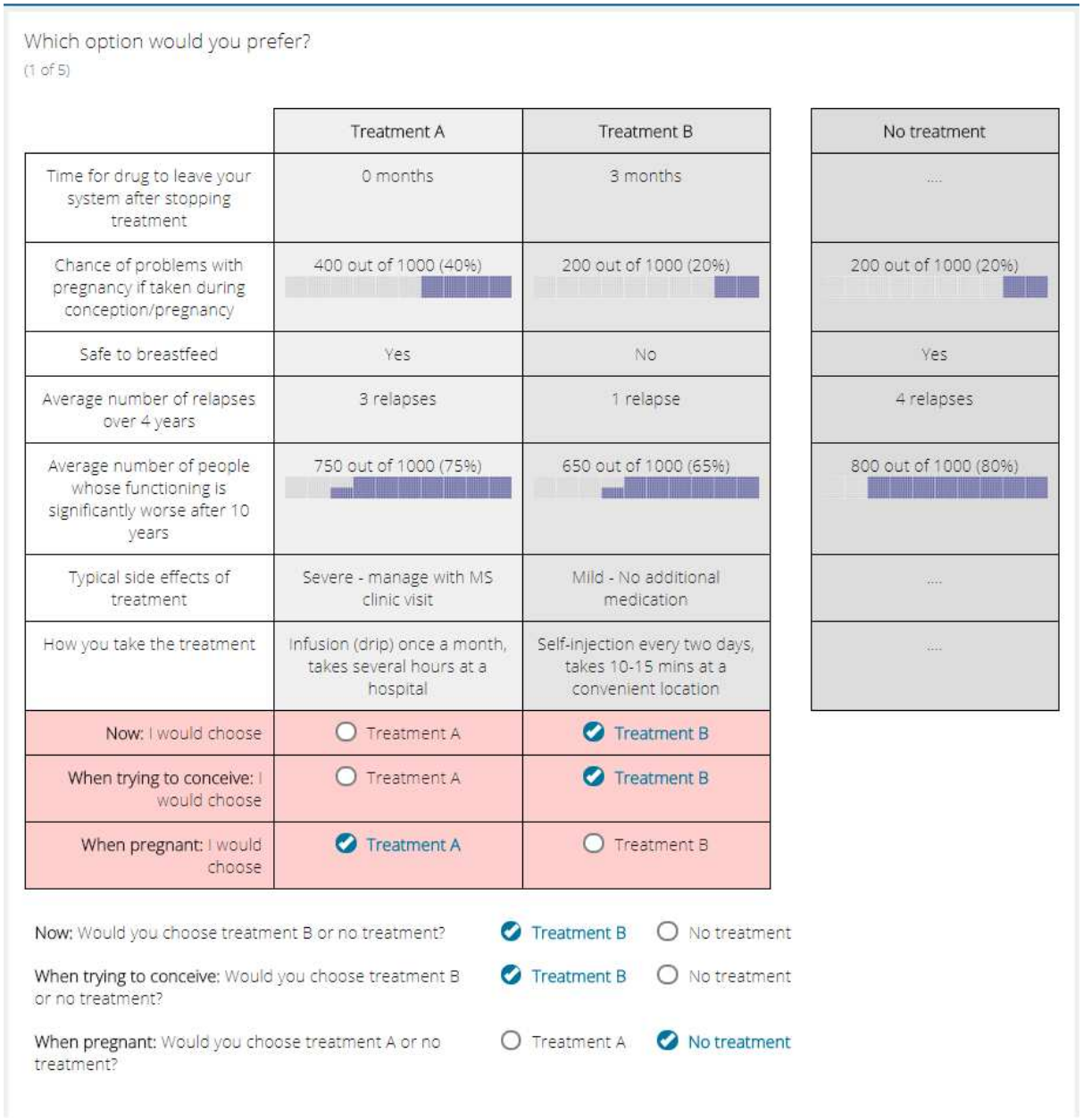

Figure 2: Illustration of how scenarios were presented sequentially. Each subfigure shows the additional task which was presented after participants responded to the previous task.

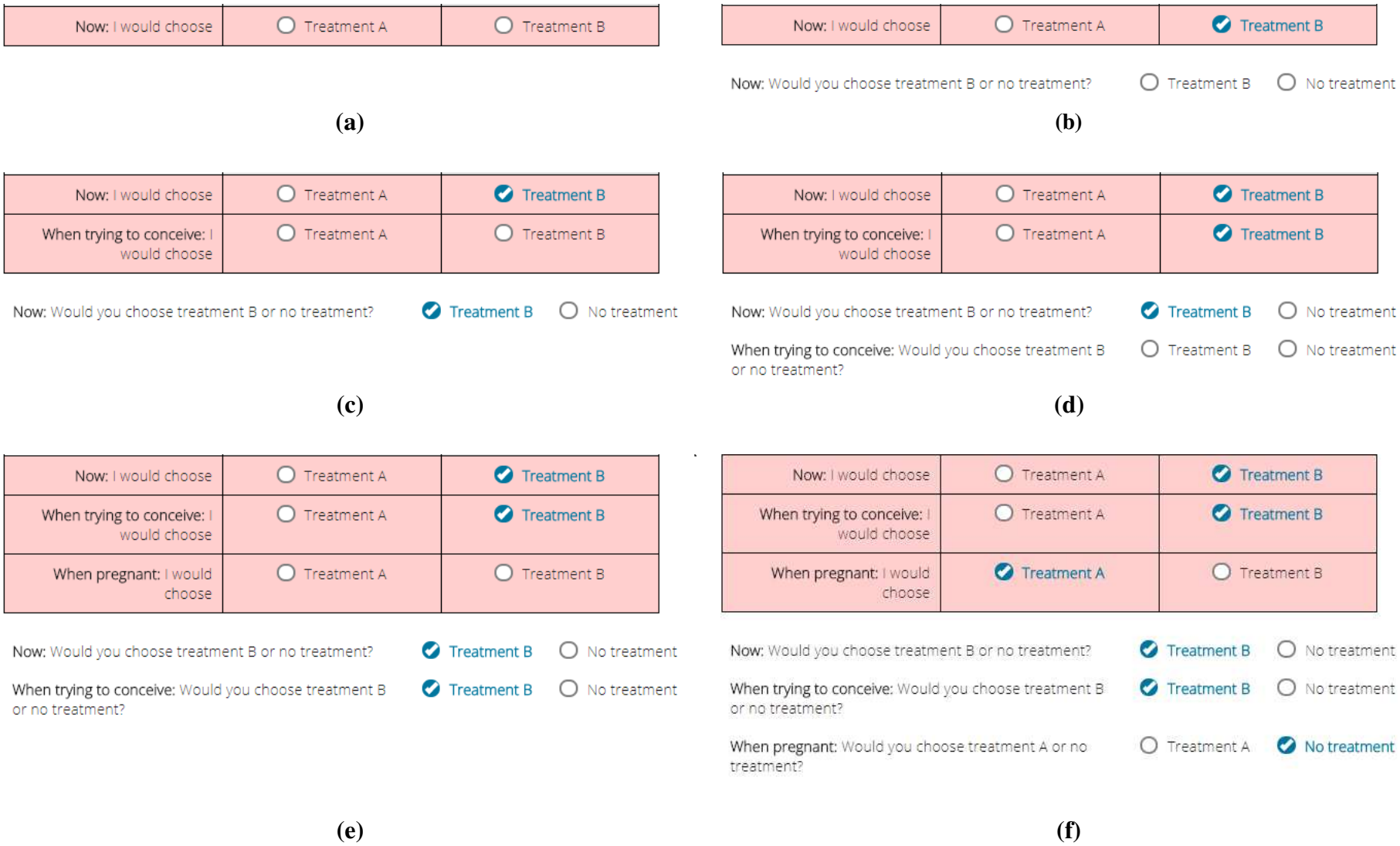

Figure 3: Maximum acceptable risks of problems with pregnancy for other attributes. Error bars show 95% confidence intervals.