Preventing Rheumatoid Arthritis: Understanding Factors that Influence Decisions to Take Preventative Treatments for Rheumatoid Arthritis

by

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H.B.Sc., The University of Toronto, 2015

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Pharmaceutical Sciences)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

August 2017

Abstract

Introduction

Currently, there are ongoing clinical trials for preventative treatments that aim to prevent and minimize the progression to RA in high risk individuals. However, preferences that drive people's decision making in the context of a preventative treatment are unknown. With these clinical trials reporting their results within the next 2 years, this thesis aims to understand preferences of those who are at high risk of RA around preventative treatment and guide how these preferences can be best implemented in preventative treatment programs.

Objectives

1) To identify important attributes for uptake of a preventative treatment program for those who are at high risk of RA, **2)** To identify the value that is placed on these attributes through a discrete choice experiment (DCE), and **3)** To predict the potential uptake of a preventative treatment options in those who are at high risk of RA

Methods

To determine the attributes that were important for the uptake of a preventative treatment program for those who are at high risk of RA, individuals with RA, first-degree relatives and rheumatologists were interviewed. These interviews were analyzed through a Framework Method. A DCE provided insight into whether those who are at high risk of RA would be willing to take preventative treatment.

Results

The qualitative Framework analysis of patient, first-degree relative, and rheumatologist focus groups yielded five different attributes to be included in a DCE. Including the five treatment related attributes in the DCE demonstrated that first-degree relatives and RA patients preferred preventative treatments that had high risk reduction of RA, were orally administered, minor reversible side effects, moderate certainty in estimates, and were preferred by the health care provider. Predicted uptake of preventative treatments ranged from 51% to 92%, with oral methotrexate having the highest and infusion rituximab having the lowest.

Conclusion

This thesis provides understanding around preferences, and subsequent trade-offs that an at risk individual might make when considering preventative treatment for RA. Through these trade-offs, the most important attributes of a preventative treatment program have been identified, and the likely uptake of potential preventative treatments have been estimated.

Lay Summary

Currently, there are ongoing clinical trials for preventative treatments that aim to prevent and minimize the progression to RA in high risk individuals. However, preferences that drive people's decision making in the context of a preventative treatment are unknown. This thesis aims to understand preferences of those who are at high risk of RA around preventative treatment and guide how these preferences can be best implemented in preventative treatment programs. Those at high risk of RA preferred preventative treatments that had high risk reduction of RA, were orally administered, minor reversible side effects, moderate certainty in estimates, and were preferred by the health care provider. Predicted uptake of preventative treatments ranged from 51% to 92%, with oral methotrexate having the highest and infusion rituximab having the lowest.

Preface

This dissertation (including the initial design, conception, analyses, and written work) is an original, unpublished intellectual product of the author, Luke Spooner. The studies conducted as part of this work were reviewed and approved by the UBC Behavioral Research Ethics Board (BREB) under ethics certificate number H07-03088.

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DCE – Discrete Choice Experiment

DMARD - Disease Modifying Anti-Rheumatic Drug

FDR – First Degree Relative

RA – Rheumatoid Arthritis

Acknowledgements

I would like to thank my thesis supervisor Dr. Mark Harrison for his support, patience, mentorship and guidance. My UBC experience has been phenomenal because of this.

I am grateful to all of my committee members Dr. Nick Bansback, Dr. Larry Lynd, Dr. Kam Shojania, and Dr. Shyh-Dar Li for providing their valuable insights and feedback on my thesis studies.

I would like to thank my wonderful colleagues especially Katherine Milbers at Collaborations for Outcomes Research and Evaluation who helped me with my research, develop as a graduate student and a person.

Lastly, I would like to thank my parents Angela and Gordon, siblings Jayne, Paul, Sean and Mark, grandparents William and Eugene, and Kathy for their support throughout my undergraduate and masters degrees.

Chapter 1: Introduction

1.1 Thesis Overview

1.1.1 Research Statement

This thesis aims to explore the preventative treatment preferences of individuals predicted to have a high risk of developing rheumatoid arthritis (RA). By understanding these preferences, and subsequent trade-offs that individual's make, it is possible to identify the most important attributes of a preventative treatment program and the emphasis placed on these attributes, predict the acceptability of potential treatments for different risk groups, and estimate the likely uptake of a preventative treatment program.

There are multiple predictors of developing RA including family history (1), sex (2–4), smoking (5,6), obesity (7), ethnicity (8–10), and presence of various antibodies such as rheumatoid factor (RF) (11), anti cyclic citrullinated peptide (CCP) (12), and anti-citrullinated protein antibodies (ACPA)(13). The development of RA occurs in phases, starting with genetic risks such as family (1) and sex (2–4). Environmental factors such as smoking (5,6), obesity (7), and exposure to toxic chemicals (14,15) can over time further elevate this risk of developing RA. Before the onset of RA, there is an asymptotic phase where RA specific antibodies such as CCP (12) and RF (11) may be present and elevated. Following this phase, there may be a period of stiffness, inflammation, and pain in the joints which is then classified as either undifferentiated arthritis or RA. The current standard of practice is that once this phase is reached, it is essential to begin DMARD treatment to prevent joint damage and disability.

Knowledge of these risk factors for the development of RA, offers a potential window of opportunity to screen and identify those who are at high risk of RA. There have been several prediction models developed based on these risk factors in an attempt to predict who will develop RA in at risk populations (16–20). In one study with patients experiencing arthralgia and testing positive for RA related antibodies, 43% of those classified as high risk developed inflammatory arthritis within a year compared to 3% in the low risk group (13). Another study involving patients who were anti-CCP positive with non-specific musculoskeletal symptoms, 41% of those classified as high risk developed inflammatory arthritis within a year compared to 0% in the low risk group (15). These findings suggest that though prediction models may be able to rule out who won't develop RA, there is still uncertainty around if those classified as high risk for RA by these prediction models will actually develop RA. Additionally, given that these models were developed in individuals with some symptoms of joint pain and swelling, there is limited evidence of the diagnostic performance of risk predictions algorithm in asymptomatic populations which would be the focus of a potential preventative treatment programs(21).

Using these prediction models, those who are at high risk for RA could potentially be identified and offered preventative treatment to delay or prevent the onset of RA. Since smoking (5,6) and obesity (7) are known predictors of RA, lifestyle changes such as smoking cessation and weight loss programs may be non-pharmacologic ways of reducing the risk of RA. Possible pharmacologic interventions for preventative treatment include statins (22), intra-muscular steroids (23), non-biologic disease-modifying anti-rheumatic drugs (DMARDs) (24) and biologic DMARDs (25). However, despite recent developments in the ability to predict and prevent RA, there is very limited evidence about the effectiveness of these preventative treatment options.

Clinical trials being undertaken in both Europe and the USA are evaluating the effectiveness of preventative treatment in delaying or stopping progression of RA in high risk individuals (26,27). With these clinical trials reporting their results within the next 2 years, this thesis aims to understand preferences for preventative treatment programs to guide how these results can be best implemented.

1.2 Overview of Thesis Themes and Chapters

This thesis focuses on the development and analysis of a discrete choice experiment (DCE), which was designed to elicit the preferences of individuals with RA, and asymptomatic individuals with relatives diagnosed with RA, with regard to preventative treatment programs for those identified to be at high risk of developing RA. DCEs describe goods or services using attributes and their levels. For example, an attribute of a good or service could be color and its different levels could be blue, green, yellow, etc. When completing a DCE, individuals are asked to choose between different sets of hypothetical choices described by different levels of the same attributes. The development of the DCE is described in Chapter 2 "Perspectives of Patients, First-Degree Relatives and Rheumatologists on Preventative RA Treatments: A Qualitative Analysis", which focuses on identifying the important attributes which describe the key considerations around preventative treatment options. Perspectives in this chapter include *ex post* patient perspectives and *ex ante* first-degree perspectives of first degree relatives of patients, and also of physicians/health care providers who might be expected to deliver a preventative treatment program. These attributes were elicited through a qualitative framework analysis of transcriptions of RA patients, first-degree relatives or RA patients (referred to hereafter simply as first-degree relatives) and rheumatologist focus groups. In the design phase of a DCE, qualitative work has been recommended, especially for the identification of attributes and levels to be

included (28). Additionally, there is currently no literature which describes the decision-making process or examines the important attributes of preventative treatment program for RA from the perspectives of these key groups. This qualitative analysis fills this gap in literature and is unique in providing insight from multiple stakeholders. This includes rheumatologists who may be expected to support decisions of the individuals at high risk of RA for whom a preventative treatment might be recommended, first-degree relatives who are a proxy for those at high risk of RA (since genetics are a key risk factor for RA), and patients who may be involved in the decisions of their at-risk relatives because of their experience with the disease and the types of treatments that may be offered.

Once the key attributes are identified and described, the value that is placed on these attributes by these groups and the estimated uptake of preventative treatment in those that are at high risk of developing RA is the focus for **Chapter 3** of this thesis, and elicited using a DCE. Through combination of these qualitative and quantitative studies, the most important attributes of a preventative treatment program, the value that is placed on these attributes, and the likely uptake of preventative treatment has been addressed.

The relevant background and rationale for these studies are outlined in the **Chapter 1** of this thesis. **Chapter 2** is a Framework Analysis of focus groups including patients, first-degree relatives of patients, and rheumatologists to identify the most important attributes of a preventative treatment program for RA. **Chapter 3** then presents these attributes in a DCE study to obtain the preferences for and relative value of each attribute. The DCE results identify the necessary features treatments require for the successful uptake and implementation of a

preventative treatment program for RA, or why current treatments under study will unlikely meet the requirements of those asked to consider preventative treatments. The final **Chapter 4**, summarizes findings from the Framework Analysis and DCE, discusses strengths, limitations, relevant applications, and future directions for research.

1.3 Delivery of Health Care in Canada

Health care financing and coverage varies significantly by country. Depending on the country, health care is provided publically, privately, or through a combination of both. Health care in Canada is delivered provincially through a universal public insurance program. In this universal public insurance program, health services are provided at no cost however there are some non-covered benefits including drugs, dental care, and optometry. These non-covered benefits are covered through private insurance or paid out of pocket. Around 67% of Canadians have private insurance, provided usually by employers or government drug benefit plans. Government drug benefit plans cover seniors, social assistant recipients, and diseases or conditions with high drug costs. Depending on insurance coverage, the amount individuals pay out of pocket for medication varies greatly. These out of pocket costs for medications can have a significant impact on access to health care as some individuals are able to pay for these costs while others are not able to. Therefore it is important to ensure in a health care system that medications that are prescribed are affordable. Lack of affordability may lead individuals to choose not to take treatments because of the costs associated with them which can have serious consequences on their overall health.

1.4 Rheumatoid Arthritis

RA is a chronic systemic inflammatory disease that primarily affects the joints. RA is described as an autoimmune disease because instead of the immune system attacking pathogens and viruses, it attacks normal healthy tissues. In RA, the tissue primarily attacked by the immune system is the synovial membrane which leads to inflammation manifested by pain, warmth and swelling (29). RA most commonly affects the joints, specifically the fingers, wrists, knees, ankles, and feet. If untreated RA untreated can also affect the eyes, lungs, skin, heart and the nervous systems (29). Early symptoms of RA include symmetrical joint swelling, morning stiffness and tenderness, and over time these can eventually lead to irreversible joint destruction (29). RA is associated with increased cardiovascular risk and increased mortality (30,31).

1.5 Epidemiology and Burden of Rheumatoid Arthritis

In the developed world, between 0.5-1% of adults are affected by RA (32). RA affects the lives of over 330,000 Canadians and is estimated to cost more than $2 billion in yearly direct healthcare costs alone (33). The estimated indirect costs of RA are more than $3 billion per year from presenteeism, absenteeism, and reductions in labour force participation (33). With the aging Canadian population, the number of Canadians diagnosed with RA is expected to increase to an estimated 550,000 in 2040, approximately 1.3% of the Canadian population (33). RA can occur at any age, however incidence rates of RA significantly increase with age (4), and peak incidence rates are in the 55 to 64 age group in women (59.4-135.5 per 100,000 persons) and 65-74 age group in men (31.9-97.8 per 100,000 persons) (4). RA has higher incidence and prevalence rates in certain sub-groups of the population including women (2–4) and First Nations (10,34,35). Studies have found incidence and prevalence rates of RA in women are

approximately 2-3 times higher compared to men (2–4). In First Nations populations, RA occurs at least twice the rate of the general population (35), at an earlier age (9), and with increased severity (9).

1.6 Risk Factors for Rheumatoid Arthritis

There are many risk factors for RA including genetic, environmental, lifestyle, and clinical factors (36). The risk of developing RA is predisposed by genetic risks such as family history of RA (1), female sex (2–4), and ethnicity (8–10). There is a strong genetic component to RA, with an approximate heritability for seronegative RA estimated to be 20% and seropositive RA to be 50% (37). People with a first-degree relative with RA have between 3 to 9 times greater risk of developing RA compared to the general population (1). Gender is also a significant risk factor given that incidence rates of RA are 2-3 times higher in women (2–4). Lastly, given that RA occurs in First Nations at least twice the rate of the general population, First Nations ethnicity is a risk factor for RA (32).

Though the risk of developing RA begins with genetic risk factors, this risk can be increased through lifestyle choices such as smoking (5,6), obesity (7), red meat consumption (38), and excessive coffee consumption (39). Many studies have found that smokers have significantly greater odds (1.7-1.8) of developing RA compared with non-smokers (17-19). These odds were found to increase significantly with each pack year (20 cigarettes a day) smoked, suggesting a dose-response relationship between smoking and the risk of developing RA (18-19). Obesity has been linked to the risk or RA; those who were obese (BMI>30kg/m^2) had between 2.1-3.7 higher odds than those who were not obese (17,20). There is also evidence that in addition to increasing

the risk of RA, obesity can decrease the age of RA onset (20,21). Consumption of red meat (38) and coffee (39) have been found to be associated with higher risks of developing RA, although it is currently uncertain whether there may be some factor closely linked with consumption (e.g. smoking) rather than the actual consumption itself. Several lifestyle factors and choices were identified to reduce the risk of RA including moderate alcohol consumption (40), omega-3 fatty acids (41), and adequate vitamin D intake (42).

In addition to lifestyle choices increasing or decreasing the risk of developing RA, there are also environmental factors associated with an increased risk of developing RA. Generally, these environmental factors are related to occupation, such as exposure to silica dust (43), which is present in many construction materials including rock, concrete, soil and sand, and organic solvents (44) such as paint or nail polish remover, textile dust (45), and pesticides (46). These are generally associated with occupations such as farmers, upholsterers, textile manufacturing and hair-dressers (44,45,47). Exposure to these occupational based factors has been found to increase the odds of developing RA between 1.4 - 2.8 times (43–46). Non-occupation based exposures that have been suggested to increase the risk of RA include air pollution (48,49) and geographic location (50,51). A recent study found living closer to major roads or highways, a proxy for higher pollution levels, was associated with an 31% increased risk of developing RA (48).

Finally, there are clinical factors that predict the development of RA, including the presence of various antibodies and cytokines such as RF (11) and anti CCP (12). One study found that in those who have these antibodies present in their blood, 28–34% of RF, 34% of CCP2, and 41% of CCP1 developed RA later on (12,52). Other studies have found that the presence of these

autoantibodies and cytokines are most likely to be precede RA many years before diagnosis, are highly specific to RA, and accumulate before the onset of RA (12,53,54). One study found that the autoantibody 14-3-3η was present in 90% of early RA patients and combined with RF and anti CPP could identify almost 95% of early RA patients (55).

Ultimately, these risk factors contribute to the development of RA in multiple hit process (36). The process begins initially with having genetic risk factors, then continues overtime with exposure to lifestyle and environmental risks, and lastly becomes apparent clinically with the development of various antibodies and cytokines. Given these multiple phases before progression to RA, those with significant risks of developing RA can potentially be targeted for preventative treatment to delay or prevent the onset of RA.

1.7 **Diagnosis of Rheumatoid Arthritis**

RA can be difficult to diagnose because symptoms gradually accumulate over time and are rarely present in early RA (56). There may be also be significant periods of time between symptom onset and seeking medical health and between receiving medical help to diagnosis (57). Delays in the early treatment of symptoms can lead to significant joint damage, disability, and increased disease activity which not only reduces quality of life but also increases the risk of comorbidities and early mortality (58). The difficulties in identifying earlier stages of RA were drivers behind the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) developing new criteria for "definite RA" in 2010 (59). These criteria include the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis to explain the synovitis, and a total score of 6 or more out of 10 from individual scores in 4

domains (number and site of involved joints, serologic abnormality, elevated acute-phase response, symptom duration) (59). Compared to the 1987 criteria, the 2010 criteria had higher sensitivity (increased ability to identify those who had RA) but lower specificity (lower ability to identify those who don't have RA) (60). Though the newer criteria does improve the ability to identify RA, it has been mentioned in literature that there may be patients who would be classified as having RA using the 1987 criteria but not the 2010 criteria largely due to the requirement of testing positive for either RF or anti-CCP (61).

1.8 Screening and prediction of RA

Multiple studies have shown that RA has a prolonged asymptomatic preclinical phase of development (62–64). During this phase there are increased levels of biomarkers including cytokines, C-reactive protein, and rheumatoid factor (62–64). However eventually, this asymptomatic preclinical phase transitions to into RA, and throughout this transition symptoms gradually begin to emerge (21). Generally the first symptoms to appear in this preclinical phase are musculoskeletal symptoms such as joint pain and warmness which are then followed by chronic joint swelling (65). Screening for biomarkers such as anti-CCP and RF in this preclinical phase in addition to monitoring these symptoms offers the opportunity to identify and treat high risk individuals early, and possibly prevent the development of RA(66).

Though there is the opportunity to prevent RA by screening for these markers and monitoring symptoms, there is still uncertainty around the ability of these markers and symptoms to predict future RA. Some of the potential tests such JOINTstat^{TM}(67) and anti-citrullinated protein antibodies (ACPA)(13) have been shown to be highly specific for RA and could be used to

predict RA in asymptomatic individuals. In addition to these tests, evidence suggests that genetic tests could be used predict RA in high risk individuals, however these tests have limited sensitivity, meaning that some of those who classified as high risk for RA may not go on to develop RA (68). However, combining both genetic and clinical factors with additional factors such as age and sex improves the predictive ability, but even with these additional factors prediction models might not be able to entirely predict who will and will not develop RA(21). Van der Helm-van Mil et al. (66) created a 14 point prediction score based on these screening and clinical factors in undifferentiated arthritis patients. Those with a score of 5 or above had a 49% 1 year probability of developing RA, while those with a score of 8 or above was associated with a 95% 1 year probability of developing RA (66).

These results show that it is difficult to predict who will develop RA without collecting a substantial number of screening and clinical factors. Additionally, with screening, tests will vary in specificity, sensitivity, positive and negative predictive values. Specificity refers to how well a test identifies those that are not predicted to develop RA whereas sensitivity refers to how well a test identifies those who are predicted to develop RA. If tests have high sensitivity and low specificity they will identify all those who will go on to develop RA however there will also be a high number of false positives. If tests have low sensitivity and high specificity, there will be a low number of false positives however there will be a high number of false negatives. The positive predictive value of a test refers to the probability that an individual with a positive result will go on to develop RA while a negative predictive value refers to the probability that an individual with a negative result will not go on to develop RA. A summary of sensitivity,

specificity, positive and negative predictive values and how they are calculated can be found in **Table 1-1.**

Table 1-1: Summary of Sensitivity, Specificity, Positive and Negative Predictive Value

	Will Individual Develop RA?	
	Yes	No
Test Result Positive	**A** 10 (True Positive)	**B** 5 (False Positive)
Test Result Negative	**C** 6 (False Negative)	**D** 3000 (True Negative)

Sensitivity= TP/(TP+FN) = 10/(10+6) = 63%

Specificity= TN/(FP+FN) = 3000/(3000+5) = 99%

Positive Predictive Value= TP/(TP+FP) = 10/(10+5) = 67%

Negative Predictive Value= TN/(TN+FN) = 3000/(3000+6) = 99%

There will be some false positives and negatives, leading to some who go on to develop RA not receiving treatment and some who would not go on to develop RA receiving treatment. Any treatment offers risks of side effects. Nevertheless, despite these risks of a false positive or false negative, in regards to preventative treatment there may be some individuals that are high risk for RA that are willing to accept these risks in order to prevent RA.

1.9 Preventative Treatment for Rheumatoid Arthritis

There are a number of existing and ongoing studies evaluating the ability of treatments to prevent RA in asymptomatic individuals. A clinical trial that included patients with undifferentiated arthritis found that methotrexate delayed progression to RA in a small proportion of patients, however it was suggested that there are no lasting long-term benefits (69).

A reanalysis of the trial data suggested that this finding was caused by the inclusion of individuals in the trial who were not necessarily at high risk to develop RA (70). In some of those who were at high risk of developing RA, methotrexate prevented progression to RA in about 45% of patients compared to 0% for placebo over a period of 5 years (70). This finding suggests that there may be a significant benefit of providing early treatment for RA in this high risk population. A limitation of this reanalysis was the small sample size in each of these groups, however this finding suggests that if these treatments are given to the right population the opportunity for preventing RA using non-biologic DMARDs is promising(70).

There are a number of proposed early treatments for RA. These range from statins (22), intra-muscular steroids (23), non-biologic disease-modifying anti-rheumatic drugs (DMARDs) (24) and biologic DMARDs (25). Each of these proposed treatments will likely have considerably different likelihoods of preventing RA, risks of harms, levels of evidence supporting the long term potential risks and benefits, as well as differing methods and frequency of administration, and varying costs. Of these proposed preventative treatments, non-biologic DMARDs and biologic DMARDs are currently being tested in clinical trials specifically in high risk individuals (26,27,71). Preliminary results from biologic DMARDs trials including rituximab and abatacept in individuals that were high risk for developing RA are promising (72,73). The Prevention of RA by Rituximab (PRAIRI) study showed that Rituximab can potentially delay the onset of RA and have a preventative effect (72). Development of RA in the rituximab group occurred at a median time of 24 months compared with 12 months in the placebo group (72). Furthermore, the risk of developing RA at 12 months was reduced by 55% in the rituximab group compared to placebo (72). Another trial Arthritis Prevention in the Preclinical Phase of RA with Abatacept

(APIPPRA) in which individuals that were high risk of RA were treated using abatacept for a period of 6 months found that at 12 months 46% of the treatment group developed RA compared with 67% for placebo (73). Currently there are no trial results for DMARDs, however there is an ongoing clinical trial (STOP-RA) in high risk patients using hydroxychloroquine (HCQ), a non-biologic DMARD, scheduled to report in March 2020 (26).

Though clinical trial results for the preventative treatment of RA are promising, it is important to recognize that there are also risks associated with these proposed medical treatments as well as potential benefits. There is a risk that any of the proposed preventative treatments may not prevent, delay or reduce the risk of developing RA in certain individuals, meaning that they are exposed to potential side effects from the preventative treatment with no potential to benefit. Side effects can also vary in severity and length, some may be less severe and reversible while others may be serious and irreversible. Common side effects of methotrexate include nausea and vomiting while more some of the more serious and rare side effects include acute hepatitis, osteoporosis, and dysphoria (74). Biologic DMARDs also have side effects, with infections being one of more common less severe side effects, while pneumonia and myocardial infarctions being more severe and rare side effects (75,76). Differences between the side effects and potential effectiveness of preventative treatment highlight the importance to understanding whether, in the presence of these risks, people who are at high risk of RA would considering taking these preventative treatments.

1.10 Understanding the Trade-offs Individuals Make in the Decision to Take Treatment

It is important to consider the risks and benefits in both the diagnostic test and potential treatments when deciding whether to take preventative treatment for RA. DCEs are a way of understanding the tradeoffs between and value placed on these risks and benefits, as well as other attributes of a treatment. In economic evaluation and decision making, DCEs have become commonly used for understanding preferences and predicting choices (77). This is because DCEs reduce decision making to a set of attributes and provide understanding of the trade-offs that individuals make between these different attributes (78). DCEs also allow for the simulation of a future market to determine how individuals might behave in it. DCEs are based on random utility theory, which assumes economic rationality and maximization of utility (79). This means that when making a decision, it is assumed that an individual will choose the option that provides what they consider to be the highest individual net benefit, often referred to as a utility (77). Lancaster states that this overall utility for a good can be described by the utilities of each individual attributes of which it is composed, and the levels of these attributes (80).

Well-functioning markets exist when there is no market power on the supply and demand sides, the information necessary for both consumers and producers to make informed decisions, and no externalities. In a well-functioning market, because it is assumed that individuals make decisions that will maximize their utility, revealed preferences can be used to determine the utility of a good or service. However, if markets don't exist (e.g. ahead of launch), or a well-functioning market does not exist due to market failure occurs it is difficult to determine the true preferences of individuals. Market failure occurs in health care occurs for numerous reasons including that there is a demand for health instead of health care itself, asymmetry of information between the

users (patients) of the health care system and the providers (physicians), caring externalities, distortion of health care prices by health insurance (i.e. users do not pay the full price for services), and no competition between health services. As well, patient decisions are also heavily influenced by perceived risks and benefits, personal biases, health care provider, and past and present experiences with the health care system. Additionally in healthcare, there are also treatments that may not yet currently exist or that are under development, and the outcomes of these treatments are uncertain and in the future. Hence, stated preference (what individuals say they would do) rather than revealed preference data (what individuals actually do) is often the next best alternative. Therefore, for this reason, DCEs have become commonly used to understand healthcare and treatment preferences, and even their acceptability in practice before they are implemented.

Typically, in DCEs, individuals are asked to choose between different sets of hypothetical choices. In a preventative treatment program for RA, potential choices could include non-biologic DMARDs (e.g. methotrexate, hydroxychloroquine) and biologic DMARDs (e.g. rituximab, abatacept). Generally, each choice can be described by a group of attributes that can be either numerical or categorical. Numerical attributes in this example could include cost ($10, $1000, $4000), frequency of administration (daily, weekly, monthly) and risk reduction of RA (10%, 20%, 40%) while categorical attributes could include method of administration (tablet, injection, infusion) or opinion of the health care provider (recommends, indifferent, does not recommend). These attributes and their levels are likely to be different for various non-biologic and biologic DMARDs, and other preventative treatment options. Creating choice sets where attribute levels vary forces individuals in the DCE to make trade-offs between these attributes

when making a choice between two treatments. These choices then can be examined to understand the importance of the attribute and/or its levels in the decision-making process, or in this case choosing a preventative treatment for RA.

1.11 Discrete Choice Experiments in Rheumatoid Arthritis

In RA, DCEs have been administered to the general population (81), those at high risk of developing RA(82), patients (83–85), and rheumatologists (86), with the majority focusing on treatment preferences (81–85). Of the three DCEs that have been administered to RA patients (83–85), only one has included early RA patients (85). This DCE, which aimed to elicit treatment preferences for early RA patients, found that early RA patients mainly focused on symptom improvement, followed by a reduction in the risk of developing serious joint damage (85). These preferences in early RA patients are different compared to long term RA patients who valued the risk of an adverse event (84) and dosing schedules (83,84) over treatment benefits. In a general population setting, benefit and risk of side effect in treatments were valued but also the route of administration (81). In a DCE seeking the preferences of those at high risk of developing RA, treatments that had high reduction in the risk of developing RA and low risk of a serious side effect were preferred (82).

The sole study of preferences for preventative treatment in high risk population had a number of key limitations. This study did not use focus groups to derive the attributes of the DCE that was administered to this population, raising concerns that the attributes included may not either be comprehensive (i.e. not all relevant attributes are included), or relevant (i.e. there are some attributes that might not be important are included) to this population. Additionally, the analysis

did not allow for the understanding of tradeoffs made between treatment attributes because it only provided the binary choice of choosing treatment or no treatment. The uptake of preventative treatment was based on whether individuals would accept a treatment with certain attributes based on their risk of RA which may not be reflective of the attributes of treatments currently available. The sample size of respondents in this study was very small (n=32), though they were confirmed at risk people. Additional concerns might be that there was no visual depictions such as an icon array to communicate attribute levels. To make informed decisions in a DCE, individuals must understand the attribute levels. Visual aids can significantly improve decision making and comprehension of choice tasks especially in individuals with low numeracy and health knowledge (87). As well, visual aids can reduce numerical biases including denominator neglect (88) and framing effect (89).

These differences in preferences for RA treatment between these groups emphasize the importance of eliciting attributes and preferences through focus groups and a DCE from those who are at high risk of RA rather than assume them from prior studies. The DCE that was administered in this thesis expands upon previous work done by Finckh et al. (2016) as it uses an in depth qualitative analysis to generate attributes in relevant populations, icon arrays to improve the communication of attributes, obtains trade-off information in a large sample of at risk individuals, and predicts potential uptake of treatments that are currently under study. Furthermore this DCE also has a larger sample size, which may provide a better representation of individual of are at high risk of developing RA.

1.12 Overview and Scope of Thesis Studies

This thesis uses qualitative (Framework Analysis) to describe the important attributes in the uptake of a preventative treatment program for RA, and quantitative methods (DCE) to estimate the value placed on these attributes and how people trade these different attributes off against each other, and estimate the likely uptake of treatments currently under study. These results bring timely insights to the potential challenges in the adoption of a preventative treatment strategy for RA, and the primary requirements for its successful implementation in those at high risk of developing RA. This thesis was conducted as part of a larger research study and covers two specific analyses of qualitative (Chapter 2) and quantitative data (Chapter 3). An overview of the broader context of the research project and the items for which I was responsible is outlined in **Table 1.2**.

Table 1-2: Scope of Thesis Studies

	Completed by Study Team	Completed in Thesis Work
Qualitative Framework Analysis		
Focus Group Recruitment and Design	✓	X
Transcription of Focus Groups	✓	X
Coding of Focus Group Transcripts	X	✓
Development and Application of Analytical Framework	X	✓
Interpretation of Qualitative Data	X	✓
Thematic Development	X	✓
Attribute Development	X	✓
Discrete Choice Experiment		
Respondent Recruitment	✓	X
Development and Design	✓	✓
Analysis and Interpretation	X	✓

1.12.1 Specific Objectives of Thesis Studies

Objective 1. To identify the most important factors and attributes that will be influential in predicting the uptake of a preventative treatment program by people at high risk of developing RA

Chapter 2 utilizes a qualitative Framework Analysis approach on transcripts of focus where RA patients, first degree relatives of RA patients and rheumatologists discuss the key issues and considerations around preventative treatment decisions. This analysis will elicit the key attributes

that are likely to influence preferences, trade-offs and the uptake of preventative treatment programs for RA to be explored in the DCE.

Objective 2. To identify the value that is placed on the key attributes of preventative treatments, the trade-offs people make between these attributes, and estimate the likely uptake of preventative treatments currently under study.

Chapter 3 describes the results of a DCE administered to RA patients and first-degree relatives of RA patients. The analysis of these responses describes the value that is placed on these attributes, the trade-offs people make between these attributes, and allows the estimation of the likely uptake of preventative treatment in individuals at high risk of developing RA.

1.12.2 Qualitative Analysis of Focus Groups to Inform Attributes for a Discrete Choice Experiment

Chapter 2's Framework Analysis answers questions posed in objective 1 by identifying the key attributes involved around decisions about whether to take or commence a preventative treatment program for RA, from the perspective of individuals with RA, first degree relatives of individuals with RA (high risk individuals) and rheumatologists. Some studies have reviewed perspectives around predictive models for RA in both patients and patient's first-degree relatives (40, 41), however none to date have described the perspectives around preventative treatment, or included the perspective of rheumatologists. Understanding these multiple perspectives around preventative treatment in a contemporary study using qualitative analysis will bring detailed insight into the attributes of both the predictive models and preventative treatment program that are important to these groups, and can be included in a DCE.

1.12.3 Analysis of a Discrete Choice Experiment for Preventative Treatment Options

Chapter 3 of this thesis presents attributes identified in Chapter 2 in a DCE which aims to elicit values that patients and first-degree relatives of patients (high risk individuals) place on the attributes and how they trade-off these attributes. Through analysis of DCE responses from these groups, the important factors that would influence uptake of a preventative treatment can be identified, the willingness to trade-off a the levels of one attribute for increased benefit in another attribute can be determined and then used to predict potential uptake of different treatments currently being studied as potential preventative strategies. This analysis of DCE responses answers questions framed as part of Objective 2.

Chapter 2: Perspectives of Patients, First-Degree Relatives and Rheumatologists on Preventative RA Treatments: A Qualitative Analysis

2.1 Introduction

RA is a chronic systemic inflammatory disease primarily affecting the joints in the fingers, wrists, knees and ankles of those affected. Untreated RA, however, has systemic impacts and can also affect the lungs, skin, heart and even the brain (29). Currently, once diagnosed with RA, the disease and symptoms can generally be managed effectively. Unfortunately there is currently no cure for RA. Multiple studies have shown that RA has a prolonged and identifiable asymptomatic preclinical phase of development, where there are increased amounts of biomarkers, of which include cytokines, cyclic citrullinated peptide (CCP), and rheumatoid factor (RF) (21,36,53,90). These autoantibodies and cytokines are thought to precede the onset of RA symptoms many years before diagnosis and are highly specific to RA (12,53,54).

By combining the clinical risk factors with genetic risk factors for RA, such as family history of RA(1), female sex(2–4), and lifestyle risk factors like smoking (5,6), it is now thought that it may be possible to identify those who are at high risk of developing RA. With the identification of people at high risk of RA, there is hope that it might be possible to offer treatment in this pre-symptomatic phase to prevent or delay onset of the disease. Clinical trial results have been promising, however it is clear that despite increasing ability to identify those who are at high risk of RA, there is still considerable uncertainty when and whether those who are predicted to develop RA will actually develop RA. Whether those who are at predicted to be at high risk of RA would be responsive to preventative treatment adds a further layer of uncertainty.

Given these challenges of predicting the development of RA in individuals, as well as the risks and benefits inherent to treating those at high risk of developing RA; understanding perspectives of RA patients, first-degree relatives of RA patients, and rheumatologists around predictive tests and preventative treatments for RA could provide insight as to what the pre-requisites of a preventative treatment program might be for individuals at high risk of developing RA. Engaging with those who are directly affected by the treatment can yield 'richer' and more complex attributes compared to relying solely on experts and research studies (91). To obtain attributes to include in a DCE, qualitative methods are recommended in populations that are representative of those who might be asked to make the decisions (92); in this case to recommend, consider, and provide/accept preventative treatment. Without undertaking qualitative work in these populations before administering a DCE important attributes could be excluded or attributes could be communicated in a way that is not relevant or understandable by DCE respondents, potentially resulting in inaccurate or biased DCE results (91).

The qualitative methods suggested for obtaining DCE attributes include interviews, focus groups, and meta-ethnography (91), Each of these methods have advantages and disadvantages—they vary in length of time necessary and some include more diversity in responses than others (91). Given that there are likely to be many different perspectives around choosing preventative treatment, focus groups offer the advantage that many different perspectives can be heard, as compared to alternative options such as one-on-one interviews. This rationale supported the choice to conduct focus groups instead of using other potential methods. The aim of the focus groups was to obtain the key attributes likely to be involved in

decisions around whether or not to take preventative treatment that could be included in the DCE from the key participants in decisions about whether or not to take preventative treatments for RA, which included first-degree relatives, patients, and rheumatologists. A Framework Method (93) was used to identify the key themes emerging from each of the interview transcripts and compare and contrast these across focus groups of patients, first-degree relatives and rheumatologists. This approach is systematic and allows for thorough summaries of key focus group themes from patients, first-degree relatives, and rheumatologists. The thoroughness of the Framework Method approach prevents key attributes from being excluded from my DCE, as well providing insight about how the identified key attributes should best be described to DCE respondents.

2.2 Methods

2.2.1 Setting and Participants

Rheumatologists, RA patients, and first-degree relatives of patients diagnosed with RA were recruited between January 2016 and March 2016 to participate in focus groups.

Patients and first-degree relatives were recruited through the marketing and communications lists of the Arthritis Consumer Experts/Joint Health group (Cheryl Koehn, Director, is a collaborator of the study) and the Arthritis Research Canada patient advisory board mailing list (Dr. Harrison and Dr. Bansback are affiliates of this group, and conducted in Vancouver, British Columbia. Rheumatologists were recruited through personal invite by the PIs via the Arthritis Research Centre for Canada (Dr. Harrison and Dr. Bansback are affiliates of this group) and the McGill University Health Centre (via co-PI Dr. Marie Hudson), and a single focus group was conducted at the Canadian Rheumatology Association Annual General Meeting 2016. The rheumatologist

focus group was held between the first and second round of patient and first-degree relatives focus groups.

In total, 5 focus groups (2 each in patients and first-degree relatives, 1 with rheumatologists) were conducted. A moderator who read from a prewritten promoter, then encouraged the participants to discuss and share their perspectives. All focus groups were audio recorded.

2.2.2 Focus Groups

2.2.2.1 First Round

The first round of focus groups with patients and first-degree relatives focused on several key aspects of RA and potential treatments. These included exploring the decision-making process around choosing treatments for RA, receiving feedback on a pre-prepared description of RA, determining the key attributes of treatment decision making, and potential treatment decisions around preventative treatment that should be included in the DCE. Patient focus groups concentrated on examining the instances that people had chosen a new treatment for RA—their considerations when contemplating treatment, their priorities, the information needed, and in instances of preventative treatment what information should be communicated to first-degree relatives by a rheumatologist. Following the first round and before the second round of focus groups, a focus group comprising rheumatologists was conducted to give additional insights on the treatment decisions from the perspective of those who would be potentially recommending and providing treatment.

2.2.2.2 Second Round Interviews

In the second round, a list of candidate attributes were developed from the first round interview transcripts. First-degree relatives and patient groups were given this list of candidate attributes and asked to rank the importance of attributes with regard to the decision of whether to undertake preventative treatment and to eliminate attributes that were felt to be unimportant. The second round also focused on discussing further the themes that were mentioned in the previous focus groups, and receiving further feedback on the survey design. In the first-degree relatives group, the aim was to receive further feedback on the description of RA, specifically whether the description of the survey was understandable and to gather an understanding of their feelings about how RA would or could affect their life based on what they had observed in their relatives with RA. In addition, since first-degree relatives would be one of the potential groups receiving treatment, focus was also placed on understanding the type of information the people without RA would ideally like to know when choosing whether to use preventative treatments for RA, as well as an exploration of whether uncertainty in risk prediction, benefits, and incidence of side effects were important. In first-degree relatives, preferences about whom they would want to review preventative treatment options with was also discussed.

2.2.3 The Framework Method

The method that I used for the analysis of the focus groups was the Framework Method (93). The Framework Method is a highly systematic approach which focuses on identifying similarities, differences and relationships between different aspects of qualitative data. In this process, the researcher reads through the data set, identifies sections that are relevant, and classifies them by a code. While reading through the data sets, it is important that the researcher allows for the data

to identify themes rather than from those that might have been known a priori. Once enough qualitative data has been coded, an analytic framework of codes is developed by researchers and used throughout the rest of the qualitative data. Once the coding of all qualitative transcripts is completed, a descriptive overview of the qualitative data by code is produced and descriptive themes are developed to answer the research question that is being explored.

2.2.4 Analysis of Focus Groups

Focus groups audio recordings were transcribed by a professional transcription service. Each of the interview transcripts were read and analyzed separately by two researchers (myself and Katherine Milbers) using a Framework approach (93) . The transcripts were coded by us independently line-by-line to identify important themes and messages. From these developed codes, I discussed the coding framework with my co-researcher and a qualitative methods expert (Dr. Sarah Munro) so that similar codes were consolidated into the coding framework. These codes then were grouped by importance and frequency in NVivo, a qualitative analysis software.

2.3 Results

2.3.1 Summary of Qualitative Analysis and Key Themes

In total there were 25 participants in the focus groups, 13 were patients, 5 were first degree relatives of patients, and 7 were rheumatologists (see **Table 2-1** for group characteristics).

Table 2-1: Summary of Participant Groups

Group	Number (Gender)
Patients	13 (3 Male, 10 Female)
First Degree Relatives	5 (2 Male, 3 Female)
Rheumatologists	7 (2 Male, 5 Female)

In the Framework analysis of interview transcripts 2 major themes “Living with Rheumatoid Arthritis” and “Preventing Rheumatoid Arthritis” emerged. Important subthemes and quotes for

"Living with Rheumatoid Arthritis" in each of the groups included "Being Proactive about My Health", "Wanting a Better Quality of Life", "Trying to Avoid the Side Effects of Medication, and "Having Concerns about the Impact of the Test" (**Tables 2-3 to 2-5**). Important subthemes and quotes for "Preventing Rheumatoid Arthritis" in each of the groups included "Wanting Alternatives to Medication: For preventative treatment", "Questioning if Preventative Treatment Is Appropriate", "Needing More Evidence: Due to uncertainty about the treatment", "Needing More Evidence: Due to gaps in knowledge about RA", and "Implementing Preventative Treatment for RA: In clinical practice with patients" (**Tables 2-6 to 2-7**). A summary of major themes and related subthemes is found in **Table 2-2**.

Table 2-2: Summary of Major Themes and Related Subthemes

Major Theme	**Sub-Themes**	
Living with Rheumatoid Arthritis	Living with Rheumatoid Arthritis	
	Being Proactive about My Health	
	Wanting a Better Quality of Life	
	Finding the Right Treatment for RA	
	Trying to Avoid the Side Effects of Medication	On Health (not deteriorating for patients)
		On Lifestyle (not getting worse for both patients and first-degree relatives)
	Having Concerns about the Impact of the Test	
Preventing Rheumatoid Arthritis	Wanting Alternatives to Medication: For Preventative Treatment	
	Questioning if Preventative Treatment Is Appropriate	
	Needing More Evidence	Due to uncertainty about the treatment
		Due to gaps in knowledge about RA
	Implementing Preventative Treatment for RA	In clinical practice with patients
		At the health system level

2.3.2 Key Themes

2.3.2.1 Living with Rheumatoid Arthritis

2.3.2.1.1 Patients

Patients discussed many different aspects of living with RA. Conversations focused on the impact that RA has had on their everyday lives, the side effects of the medications used to treat RA, and concerns about the impacts of a test to predict RA. The discussions patients had about the physical impacts of RA focused mainly on the joints "becom[ing] hard, swollen and stiff". Some patients discussed that without these typical symptoms of joint swelling one "might think [they] don't have the disease". Emotional impacts of living with RA were also important for patients. For example, one patient described they felt "devastated" as they "couldn't even for an afternoon get dressed, couldn't pull up the zipper on my pants". Interestingly, RA had also positively impacted some patient lives by motivating them make changes to be healthier such as exercising or quitting smoking. Side effects associated with medications were another important issue of living with RA mentioned by patients. Patients felt that taking medication for RA impacted their entire body including skin, hair, and eyes. There was a strong emphasis on the perceived damage that treatment had on their kidneys, liver, and heart, and the need to take treatments such as dialysis because of this damage. There was a wide range of discussions in the patient groups about how a preventative treatment test might impact individuals. This discussion ranged from the test being a source of knowledge, a wake-up call, and a sign to follow up with a doctor for further examination and testing rather than undertaking preventative treatment immediately.

Table 2-3: Summary of Major Themes and Related Subthemes in Patients Around Living with Rheumatoid Arthritis

	Living with Rheumatoid Arthritis	Being Proactive about My Health	Wanting a Better Quality of Life	Trying to Avoid the Side Effects of Medication	Having Concerns about the Impact of the Test
Patient	"I was just devastated, I couldn't even, for an afternoon get dressed, couldn't pull up the zipper on my pants, and I just lost so much weight."	"You want to do something about it. It's not just a matter of kind of thinking you're going to get over it"	"I had a very rich, very full no-limits life previously. I had no indication that that would change … And I would like to not have had that impeded by any kind of thoughts … I would probably choose not to try find out."	"And of course the medication is effecting all the other things, the liver, the kidneys. Your skin, your hair, like everything. Eyes."	"I'm in for taking all the tests I can get my hands on, because every little bit of knowledge helps me understand what is going on with my body. …I want to know for my own benefit these different things."

2.3.2.1.2 First Degree Relatives of Patients

First-degree relatives discussions focused on their perception of RA and the treatments for the disease, maintaining quality of life, and potential impacts of a test to predict RA. The perception of first-degree relative's around RA was very similar to patients; one first-degree relative described it as "…is it not just a disease of the joints. It just starts in the joints. It can affect every organ in your body". Some first-degree relatives discussed the effects that RA had had on their relative and the changes to the lifestyle of their relative that RA had caused; a first-degree relative describing their mothers experience with RA "she had a life and then once the disease came and took it from her, she didn't anymore". Perceptions of RA were shaped by the effects of RA on their relative. First-degree relatives discussed how they are more appreciative of their own health after having seen the effect RA has had on their relative; "it's definitely made me

more kind of appreciative of the fact that I'm healthy and I'm young and I'm able to do things without problems".

When discussing the impacts of a test to predict RA, first-degree relatives focused on whether there was a purpose of knowing how accurate the test was, and whether it would impact their insurance. Discussing the accuracy of the test focused around if there was a potential individual personal benefit, and one first-degree relative commented that "if there's nothing to benefit me there would be no purpose". First-degree relatives discussed the benefit of being able to act to prevent RA, and most individuals wanted to know "things [they] could do on [their] own to help prevent it" rather than about preventative treatment. The accuracy of the test was very important to individuals, they agreed that "a false positive or a false negative would be equally damaging for [them] in the long run" and specifically wanted to know if whether the test results could be used against them in an insurance setting.

Table 2-4: Summary of Major Themes and Related Subthemes in First-Degree Relatives Around Living with Rheumatoid Arthritis

	Living with Rheumatoid Arthritis	Being Proactive about My Health	Wanting a Better Quality of Life	Trying to Avoid the Side Effects of Medication	Having Concerns about the Impact of the Test
First Degree Relative	"She [family member] had a life and then once the disease came and took it from her, she didn't anymore. She couldn't do things."	"If there were perhaps a treatment that were extremely preventative and very effective at lessening the risk of developing such a disease, absolutely would take the test because that to me leads to something that is preventative. That leaves me being able to take some action"	"If that was a risk for the medication, it's also a risk for the RA. You're almost guaranteed to get serious infections and TB is completely likely. So would I rather get those now when I'm strong enough and healthy enough to fight them"	"Especially because of watching my mom with prednisone, if there's anything that increase the mental risk, that would be like huge for me."	"And for me adding any kind of anxiety to it, not because [a test result] necessarily jars me into a realism that I'm not comfortable with, but because I don't think it adds anything."

2.3.2.1.3 Rheumatologists

Rheumatologists were focused mainly on the impact that a test would have for high-risk individuals and challenges of managing RA in patients, especially with issues of medication adherence. Conversations around the impact the test would have for high risk individuals were focused on the cost of the test and the consequences of a positive result, including increased anxiety and potential implications for individuals' insurance costs. Describing their feelings around the challenges of patient medication adherence and managing RA, a rheumatologist felt that in even in some patients who have the disease "I feel that they've never taken them [their medications]. These are people that just never ever believe that they've actually is going to do anything to them, that they're going to have any poor outcomes".

Table 2-5: Summary of Major Themes and Related Subthemes in Rheumatologists Around Living with Rheumatoid Arthritis

	Living with Rheumatoid Arthritis	Being Proactive about My Health	Wanting a Better Quality of Life	Trying to Avoid the Side Effects of Medication	Having Concerns about the Impact of the Test
Rheumatologist	None	"They want to know because they think that they can prevent disease in themselves."	None	None	"Well, if I know I'm going to have Lupus then my insurance goes into the toilet, you know, and I don't want that, so I don't want to know. I don't want my family to know."

2.3.2.2 Preventing Rheumatoid Arthritis

2.3.2.2.1 Patients

Discussions around preventing rheumatoid arthritis in patients centered on the appropriateness of preventative treatment, the available evidence for preventative treatments, gaps in current knowledge of RA, and how to implement a preventative treatment program in practice. The appropriateness of preventative treatment in first-degree relatives' discussions centered on whether it was appropriate to provide a treatment to otherwise healthy individuals that may have the potential for serious side effects. Patients suggested to "start small" and "if the RA factor is rising then look at something" rather than immediately take medication. The availability of evidence for potential preventative treatments was also discussed. Conversations focused mainly on the dosing schedule and the potential methods of treatment administration, how it has been

tested (i.e. clinical trials), short and long-term side effects of treatment, and the evidence supporting the ability of the treatment to prevent RA. Patients were hesitant to endorse preventative treatment because they perceived that there were still significant gaps in current knowledge and ability to diagnose and understand the causes of RA. Finally, when discussing how to implement preventative treatment in practice, patients emphasized that effectively communicating why treatment needs to be taken would be a key focus for ensuring adherence. Many patients initially felt at the time of diagnosis, they were in denial of RA or that simply diet and lifestyle changes were needed rather than medication.

Table 2-6: Summary of Major Themes and Related Subthemes in Patients Around Preventing Rheumatoid Arthritis

	Wanting Alternatives to Medication: For preventative treatment	**Questioning if Preventative Treatment Is Appropriate**	**Needing More Evidence: Due to uncertainty about the treatment**	**Needing More Evidence: Due to gaps in knowledge about RA**	**Implementing Preventative Treatment for RA: In clinical practice with patients**
Patients	"Your whole generation just looks at so many different options."	"Because it's going to stop your pain when you take it anyways, why would you want to take that before if it has a lot of risk involved?"	"How the treatment affects or it works, down to a cellular level. Method, like the methods and results of testing. All possible side effects, short-term, long-term, and complementary lifestyle choices."	"If we don't know the cause, everything is suspect that we do. You know? And especially all the treatments"	"People should know why they should take the drugs because if, like for people like me who were in denial or just thought I would eat better and exercise and do yoga and whatnot I'd be fine and I don't need all these drugs."

2.3.2.2.2 First Degree Relatives

First-degree relatives focused on wanting alternatives to medication, needing more evidence about the potential treatments and current gaps in knowledge about RA. When considering

preventative treatments, some patients wanted to know if there were alternatives to treatment such as lifestyle and diet changes or natural "herbal" treatments. The evidence around potential preventative treatments was important to first-degree relatives, specifically how effective the treatments for preventing RA might be and whether the side effects would be similar and likely to occur at the same rate as those they had seen firsthand in their relatives with RA. Perceptions of current knowledge of RA discussed by first-degree relatives centered on the uncertainty with some of the different aspects of RA. This included topics such as the extent of which RA was hereditary, as first-degree relatives felt that they had received "mixed information" from various sources such as the internet and physicians. First-degree relatives also felt that rheumatoid arthritis is a "misnomer" and was easily confused with other types of arthritis such as osteoarthritis.

Table 2-7: Summary of Major Themes and Related Subthemes in First-Degree Relatives Around Preventing Rheumatoid Arthritis

	Wanting Alternatives to Medication: For preventative treatment	Questioning if Preventative Treatment Is Appropriate	Needing More Evidence: Due to uncertainty about the treatment	Needing More Evidence: Due to gaps in knowledge about RA	Implementing Preventative Treatment for RA: In clinical practice with patients
First Degree Relatives	"So let's say that it's a 60 percent chance that it's absolutely going to prevent rheumatoid arthritis later in my life, and there's a herbal treatment which is, like, 55 percent, 50 percent. That massively changes what my personal treatment plan is."	"From where it would be coming from, Dr.--- was like, "Hey, you know, there's this treatment. You know, I know how badly it effects your mother. I think that you are possibly at risk for having it," and he suggested it to me, I would definitely take a look at it."	"So that was a big sentence for me that the medications being tested in clinical trials now are the same drugs that are being used to treat people with the disease. That would strongly influence how I responded to the survey. For example, maybe if they were different drugs and they would have different side effects, and I wouldn't have to endure what my mom endures "	"And I've heard theories, everything from it skips generations to it's immediate to, you know, it only affects the women in one side of the family. I've heard a whole bunch of different crazy different things "	"there would always be that little bit in the back of my -- in the back of my mind that would go, "Okay, how far is the treatment going to be advanced by the time that I get there." You know, like in another 15, 20 years of medical science how much is the treatment for people with it going to be advanced?"

2.3.2.2.3 Rheumatologists

The main discussions in the rheumatologist focus groups were about the appropriateness of preventative treatment, the need for sufficient evidence before recommending a preventative treatment, the need for more knowledge on RA, and how a preventative treatment program would be implemented in practice. The appropriateness of preventative treatment focused on concerns about the side effects of medications; one rheumatologist described their concerns as "you have a patient who is feeling well, but the last thing you want to do is make them feel sick.". Rheumatologists felt that they would be more at ease recommending interventions that

did not have side effects, such as weight loss or smoking cessation. The quality of evidence about preventative treatment was very important to rheumatologists and their conversations focused on the probability that treatment would prevent RA, the marginal benefit of treatment compared to no treatment, and whether there was sufficient data to support preventative treatment. When discussing how to implement a preventative treatment program in practice, the concerns of rheumatologists centered on the ability to find the right group of people at high risk of RA, whether rheumatologists had capacity to take on more patients, and whether rheumatologists were well suited to provide preventative treatment interventions. Nevertheless, some rheumatologists were willing to consider providing preventative treatment in certain populations if they had enough of the risk factors, such as having a first-degree relative with RA, being a smoker, or of First Nations heritage.

Table 2.8: Summary of Major Themes and Related Subthemes in Rheumatologists Around Preventing Rheumatoid Arthritis

	Wanting Alternatives to Medication: For preventative treatment	Questioning if Preventative Treatment Is Appropriate	Needing More Evidence: Due to uncertainty about the treatment	Needing More Evidence: Due to gaps in knowledge about RA	Implementing Preventative Treatment for RA: In clinical practice with patients
Rheumatologists	"Patients want a cure, and patients want a cure naturally, right? And natural is perceived as being with no risk, which is not always true"	"But from our point of view is it safe to say though that we, too, if there was good evidence that normalizing endosmosis, or that weight loss or smoking cessation reduces, we would be more at ease with that sort of intervention than an intervention that involves medications with toxicity. So, wouldn't we also feel that way?"	"I think that a really, really strong, good solid scientific placebo control or analyzed control, let's do it, I'll push for it. But before that it is do no harm and that is how I approach my patient."	"I think that if you're able to profile rheumatoid as to those patients who have really terrible diseases, you know, you can get it under control ….. If you were able to somehow profile those patients and you were able to give something really, I would feel that those patients that I would be willing to do …If you were able to profile better RA"	"That to me is the possible place where you can make an impact just by saying if not, you know, stopping the disease, delaying the disease, the progression, to joint space narrowing and morbidity that comes with that lifestyle, indirect cost, all of those things. I think that is maybe the lower hanging fruit, as opposed to stopping it in a normal person."

2.3.2.3 Developing Discrete Choice Experiment Attributes

Through the qualitative framework analysis, I observed that the decision to consider taking or recommending preventative treatment is difficult and involves the consideration of numerous factors including the efficacy of treatment, risk of side effects, and opinions of others, especially those of a health care provider. In reviewing these factors, myself in consensus with Katherine Milbers and Sarah Munro) identified attributes and attribute-levels that would be important in considering whether to take or recommend preventative treatment. These attributes **(Table 2-9)**

identified included the accuracy of test, who recommends the person to consider treatment, the initial baseline risk of RA and risk reduction with treatment, method of administration, risk and seriousness of side effects, certainty in estimates of the risks and benefits of treatments and tests, and opinion of the health care provider. Direct quotes from patients, first-degree relatives, and rheumatologist are included in **Table 2-9** to support the selection of these attributes and provide perspectives from each of these groups.

Patient, first-degree relatives, and rheumatologist's focus group discussions underlined the importance of maintaining the well-being of those who were taking preventative treatments. Patients and first-degree relatives described a concept of well-being that was related to a desire for preventative treatments to have a minimal impact on their current lifestyle. They focused largely on wanting to know if treatments would limit aspects of their current lives such their ability to travel, maintain employment work, and participate in sporting activities. The participants of these focus groups also wanted to know whether preventative treatments would be given as a tablet or injection, require regular monitoring from a health care provider and have side effects both in the short term and long term, for them to gauge the potential impact on current lifestyle. When referring to well-being, rheumatologists focused mostly on patients avoiding the side effects of medications. These conversations suggested that the risk and types of side effects and method of administration were important attributes to include in a DCE.

Accuracy of test, risk reduction of RA, and certainty in evidence for both preventative treatments and tests were suggested as important attributes in patient, first-degree relative, rheumatologist groups. Patients and first-degree relatives discussed that they preferred high test accuracy and

preventative treatments with the greatest risk reduction, whereas rheumatologists were focused on how accurate were the individual components (i.e. genetics, presence of RA specific antibodies) of the test in predicting RA and the marginal benefit of treatment compared to no treatment. All groups agreed that the strength of evidence to support testing and preventative treatment was important, with rheumatologists especially wanting evidence from placebo controlled trials in high-risk populations.

Patients and first-degree relatives placed high value on who treatment recommendations came from, and the opinion of health care provider on both the test and preventative treatment. First-degree relatives wanted multiple perspectives from individuals who had experience with RA including patients, nurses, physicians, and rheumatologists. However, further conversations suggested that though first-degree relatives wanted multiple perspectives, their opinion on taking the test and preventative treatment would be influenced the most by "what the doctor said". Hence noting health care provider's recommendations was included as an important attribute given the emphasis placed on it by those considering the test and preventative treatment.

Table 2-9: Summary of potential attributes, their levels, and supporting quotes compiled from the Framework Analysis

Attribute Label	Lay Terminology	Key Quotations from Qualitative Data	Suggested Labels of Possible Levels
Accuracy of Test	How accurate is the test in predicting rheumatoid arthritis	"Is there some way to test how likely this thing is going to affect me as opposed to the next person?" – Patient "I guess I want to know how accurate the test is, and if there is any chance that you could maybe be told like oh, there is a very good chance of you getting it, but maybe finding out later that that actually wasn't true." – FDR "Because if you don't get IGA, for example, up to 50 percent, first degree relatives would be positive and I doubt all those are going to get arthritis, so." - Rheumatologist	**High, Medium, Low**
Who Recommends	Whether it is a health care provider, patient, or relative who recommends it	"It could be like honestly any of those things because it was just like having experience with it. Even like as a nurse having experience with it and seeing patients, treating patients, whatever, I would still just be interested in everybody's opinion." – FDR "Would learn that I had a high risk of developing RA, I would probably talk about it to people and then that is why I came up with who recommends it being important. And I think I would have to hear it from at least two sources to act on it," – FDR	**Health care provider, patient, relative**
Risk of RA and Risk Reduction with Treatment	The risk of developing Rheumatoid arthritis without vs. with treatment	"Me personally, never. Unless it's 100 percent positive. Just with the test turn out." - Patient "If there were perhaps a treatment that were extremely preventative and very effective at lessening the risk of developing such a disease" – FDR "What is the benefit? You know marginal benefit (inaudible) that in risk and so we all bought the Kool-Aid and drink the Kool-Aid that yes, everybody gets the treatment for quite a marginal benefit that there is for using this (inaudible) and then down the road see that we have other (inaudible) from that therapy when those patients were otherwise well." - Rheumatologist	**High, Medium, Low**
Method of Administration	Whether it is an infusion, injection, tablet.	"You know, I went to Europe last year with my wife. We were gone for, you know, half a year. Now if I wasn't able to do that because I had to go to a specific doctor twice a week to get this thing, no thanks. I'm good." - FDR	**Infusion, Injection, Tablet**
Risk and Seriousness of Side Effect	The risk of a side effect from treatment	"And I've had side effects with -- I had a heart attack. I had my kidneys at stage -- just the stage before. I needed to have dialysis, so. You know, there is side	**Major irreversible Minor reversible,**

Attribute Label	Lay Terminology	Key Quotations from Qualitative Data	Suggested Labels of Possible Levels
		effects that you get that you have to watch out for." - Patient "Especially because of watching my mom with prednisone, if there's anything that increase the mental risk that would be like huge for me." - FDR	**Major reversible Minor reversible, Minor reversible**
Certainty in Estimates	How strong is the evidence for the test and preventative treatments	"Whether there was enough evidence to show that that treatment actually has a chance of preventing." – Patient "Is there any data saying that coming from a high risk situation, what is the reduction" – Rheumatologist "I think that I really, really strong, good solid scientific placebo control or analyzed control, let's do it, I'll push for it. But before that it is do no harm and that is how I approach my patient." -Rheumatologist	**Moderate, Limited certainty, Very limited certainty**
Opinion of Health Care Provider	Whether a healthcare provider or patient supports/wants to take test and/or preventative treatment	"I'd be inclined to advise the person to go talk to their doctor, or read up and get familiar with it, I wouldn't advise them whether or not to take the medication right off the bat." - Patient " I think that I also have a lot of trust at this point in what healthcare professionals say. And a lot of my own opinions, and ultimately in the end, like it would be my own opinion, but I just think a lot of my own opinion would come from what the doctor said" - FDR	**Health care provider doesn't prefer, Health care provider is neutral, Health care provider prefers**

2.4 **Discussion**

Qualitative work has been recommended in the development of a DCE, however often the process of deriving attributes and attribute-levels is not reported on in literature (28). A previous systematic review of published DCEs in healthcare (254 DCEs) found that in 44% (111 DCEs) did not mention at all any use of qualitative methods (28). This chapter contributes to the existing literature by describing in detail the process of attribute elicitation through a qualitative Framework analysis.

When developing DCE attributes, it has been recommended to include those who may be involved in the treatment decision (91). In the decision on whether to consider preventative treatment, patients and rheumatologists may both be recommending preventative treatment to those at high risk of RA. Additionally, rheumatologists could be providing these preventative treatments. First-degree relatives have significantly greater risk of developing RA compared to the general population, and because of this increased risk they may be offered preventative treatment in the future (1). The involvement of these three groups in the decision to take preventative treatment was why it was necessary to include them in focus groups for the elicitation of DCE attributes and levels. Additionally, including multiple perspectives in the focus groups allows for the development of a generic DCE that can be administered to all these groups to allow for direct comparison of patient, first-degree relative, and health care provider preferences.

The qualitative Framework Analysis of patient, first-degree relative, and rheumatologist focus groups yielded seven different attributes and potential attribute levels to be included in a DCE. In the first round of interviews, patients and first-degree relatives focused significantly on maintaining their current quality of life. Suggestions on maintaining quality of life varied between patients and first-degree relatives, this variation led to many suggested attributes (i.e. risk and type of side effects, ability to maintain employment, ability to maintain an active lifestyle) that could have the potential to overlap with one another and be not mutually independent. When designing a DCE, it is important to specify attributes and their levels appropriately because the validity of a DCE is dependent on this (91,94). Further discussion of these suggested attributes in regard to quality of life in the second round, elicited two key

mutually exclusive attributes that were method of administration and risk and type of side effects. Rheumatologists also agreed that maintaining current quality of life was an important factor in the consideration of preventative treatment, though the focus of conversations were around avoiding side effects especially in the long term. Some attributes to be included in the DCE were directly identified as important in each of the focus groups. These included who recommended the treatments, the opinions of the healthcare provider, certainty in evidence, accuracy of the test and risk of RA and risk reduction from treatment. One attribute that was directly identified by both first-degree relatives and patients but excluded was the cost of the treatment and test. This attribute was excluded in our proposed DCE because costs associated with medications in Canada can vary significantly between patients depending on their insurance coverage.

A significant strength of this qualitative analysis was that it included patients, first-degree relatives, and rheumatologists, all of whom are a good representation of those involved in the decision of whether to undertake preventative treatment. Additionally, this qualitative analysis provides a detailed account of the process moving from focus group interviews to DCE attribute development an area where published literature is limited (95). Attributes elicited in this qualitative analysis were discovered through a thorough selection process involving two rounds of focus group. This prevents important attributes from being excluded or missed and avoids researcher bias which could occur if attributes were elicited from a literature review alone (91). As well, the final attributes generated from the qualitative study to be included in a DCE are reasonable (less than 10) and mutually independent.

Limitations of this qualitative study include that there was not a focus group to review the final list of attributes selected for inclusion into a future DCE. A final review of the selected list of attributes and their levels from these groups would have been valuable, however this review can also be done when piloting the DCE. Another limitation is that qualitative work generates a significant amount of data and requires significant time and resources to undertake. The large amount of data generated in the qualitative analysis, requirement for multiple focus groups, and that the qualitative work in this setting was conducted by a primarily quantitative researcher made the qualitative work time consuming, difficult, and potentially error prone. Despite these limitations and challenges, consulting with a qualitative expert (Sarah Munro) during the Framework analysis ensured that the process of eliciting of attributes was done thoroughly, efficiently and using appropriate methodology.

In conclusion, through a qualitative Framework Analysis of patient, first-degree relative and rheumatologist focus groups around preventative treatments, 7 attributes were elicited to be potentially included into a DCE, 5 relating to the treatment decision and 2 relating to the testing and referral process ahead of the treatment decision. This chapter provides insight into the process of eliciting attributes through qualitative methods. This process is often not included in published DCEs and an area of high importance. The findings of this qualitative Framework analysis will used in the development and administration of the DCE in Chapter 3, as well as in the eventual development and design of a preventative treatment program to be implemented in practice.

Chapter 3: A Discrete Choice Experiment Around Preventative Treatment Options for RA

3.1 Introduction

For those who are predicted to develop RA, suggested preventative treatments include statins (22), intra-muscular steroids (23), non-biologic disease-modifying anti-rheumatic drugs (DMARDs) (24) and biologic DMARDs (25). These treatments have different risks, benefits, dosing frequencies, and methods of administration which are known to affect treatment preferences in studies conducted in RA patients (84), patients with early RA (85), the general population (81) and exploratory studies of pre-RA groups (82). To decide between these different treatments, it is necessary for individuals to make tradeoffs between these benefits, risks and other factors associated with them. Preferences for preventative treatment have been explored previously in a group of individuals who were at high risk of RA (82), however this study excluded some of the important attributes elicited in the **Chapter 2** (certainty of evidence and preference of health care provider), did not predict the potential uptake of the treatments currently under study, was conducted with a small sample size (32 individuals), and did not communicate risk reduction through visual aids. Currently, it is not known how the attributes elicited in **Chapter 2** determine the preference of those who are at high risk of RA in considering preventative treatments. The objective of this chapter is to determine patients' and first-degree relatives preferences for attributes describing preventative treatment options, the trade-offs they make between these attributes, and predict the acceptability and uptake of potential these preventative options using a discrete choice experiment (DCE).

3.2 Methods

3.2.1 Overview

A web based DCE survey was developed using qualitative methods discussed in **Chapter 2**. Attributes to be included in the DCE were elicited through a qualitative Framework analysis of five focus groups in three separate groups of patients, first-degree relatives and rheumatologists. From these focus groups, 5 attributes directly related to preventative treatment were selected for inclusion in the DCE (**Table 3-1**). The selected attributes included centered on the risk reduction of RA from treatment, an indication of preference or otherwise of the health care provider about a treatment, the frequency and type of side effects from treatment, the method and frequency of administration of treatment, and the certainty in evidence about risks and benefits presented. Attribute levels were obtained from a literature review of studies around preventative treatments for and previous DCEs undertaken in rheumatoid arthritis, the qualitative Framework analysis in **Chapter 2**, and the characteristics of the range of available potential options for preventative treatment.

Table 3-1: Summary of Attributes and Levels for the Discrete Choice Experiment

Attribute	Attribute Label	Level	Rationale for Level
Risk of RA and Risk Reduction with Treatment	The absolute reduction of the risk of developing rheumatoid arthritis, comparing the predicted risk without and. with treatment	From 60 to 44 in 100 over 5 years From 60 to 34 in 100 over 5 years From 60 to 24 in 100 over 5 years	Based on predicted risk reduction of preventative treatments (22–27,69,70,96)

Attribute	Attribute Label	Level	Rationale for Level
Method of Administration	Whether treatment is given as an infusion, injection, tablet.	Infusion, 3-4 hours, twice 15 days apart Injection, Once weekly for 1 year Oral, once daily for 1 year;	Based on the dosing and administration of potential preventative treatment options from rheuminfo.com (97) and consultation with clinical experts (Dr. Kam Shojania and Dr. Marie Hudson)
Risk and Seriousness of Side Effect	The risk of a side effect from treatment	Common: Minor reversible, Very Rare: Major irreversible; Common: Minor reversible, Uncommon: Major reversible; Common: Minor reversible	Based on the side effect profiles of preventative treatments from rheuminfo.com (97) and consultation with clinical experts (Dr. Kam Shojania and Dr. Marie Hudson)
Certainty in Estimates	How certain is the evidence about the risks and benefits the treatments as preventative options	Very little Limited Moderate	Based on descriptions to communicate the quality of evidence published by the GRADE Working Group (98).
Opinion of Health Care Provider	Whether healthcare provider supports preventative treatment	Health care provider does not prefer Health care provider is indifferent Health care provider prefers	Attribute elicited through qualitative Framework analysis And described in a way that briefly indicates whether the physician prefers this option, does not, or is indifferent

Before administration, the survey was first piloted using members of the Sustainable Health (Dr. Harrison's research team based at UBC Pharmaceutical Sciences), the Collaborations in Outcomes Research and Evaluation (CORE) (Dr. Larry Lynd's research group, also at Pharmaceutical Sciences), and the Centre for Health Evaluation and Outcome Sciences (CHEOS, St Paul's Hospital). Changes suggested by these groups, which included several researchers experienced in the development and analysis of DCEs were incorporated. A pilot sample of 200 members of the US general population were then recruited using Amazon's Mechanical Turk (99). The pilot group reported no issues or difficulty in completing the survey in free text questions, the analysis of the pilot data resulted in co-efficients that were logically ordered, and in the preliminary analysis the results found that preferences were similar to what was expected a priori, based on other DCE studies of RA treatment decision-making.

3.2.2 Survey Design

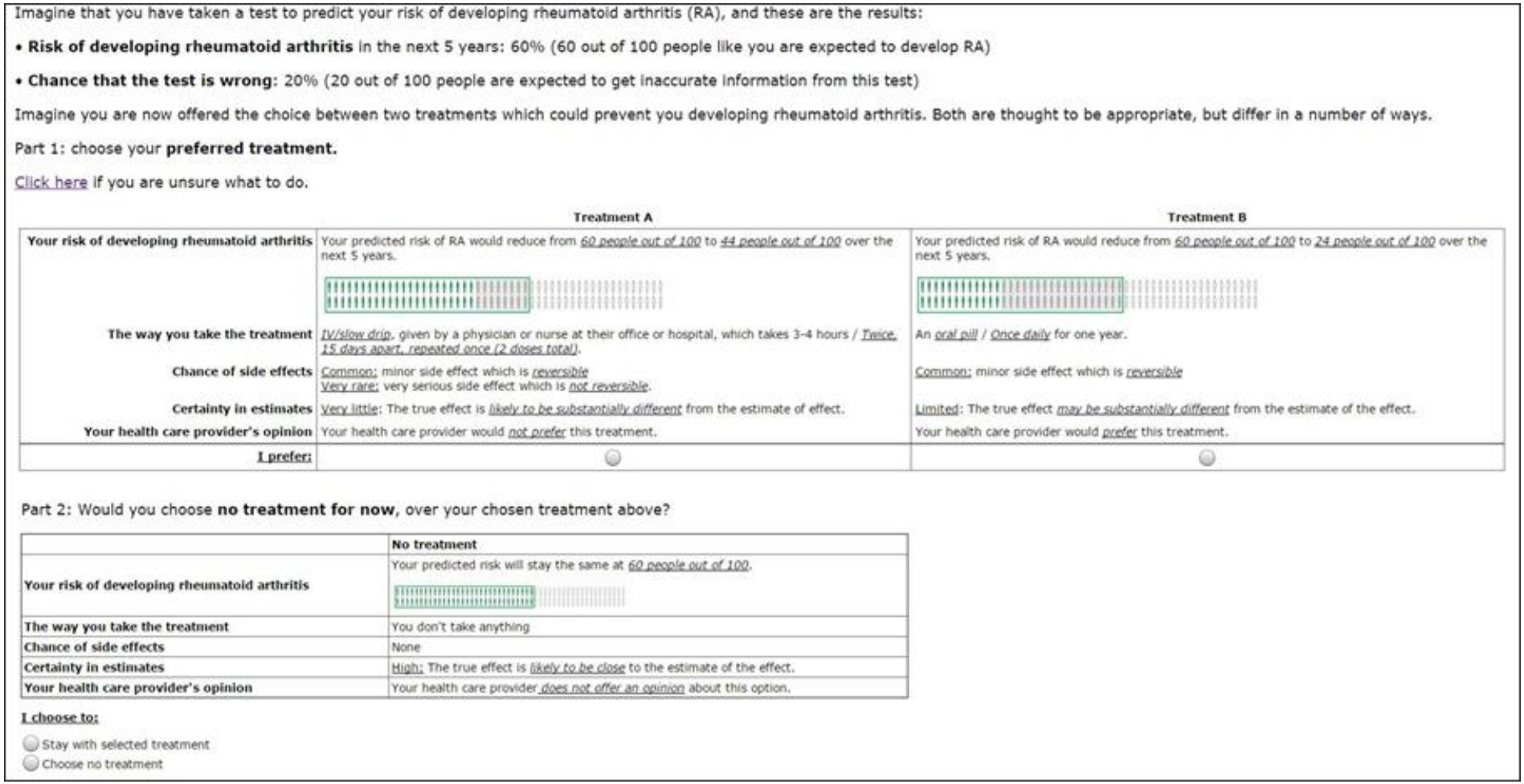
The full survey was administered either in English and French to a sample of the Canadian and US population who were either RA patients or first-degree relatives of someone with RA. The mailing list of JointHealth (100) and Amazon's Mechanical Turk (99), an online crowdsourcing tool was used to administer the survey. JointHealth is Canada's largest national patient-led arthritis organization that includes patients of all ages from the arthritis community (100). RA patients who received the survey through the mailing list were asked to complete the survey and forward it to their first-degree relative. Recruitment through Mechanical Turk was a two stage process. In the first stage, a qualification survey was released to the members of the panel. In this qualification survey, individuals were asked to self-report whether they or, in a second question, their first-degree family members, had one or more of a list of conditions which included

rheumatoid arthritis, asthma, emphysema, and heart disease, and a number of other chronic conditions. The list of pre-screener conditions also included lycanthropy (the belief that one is or can transform into an animal) as a test to screen out individuals who may not have answered the pre-screening questions accurately, for example by ticking all conditions to ensure eligibility for a survey. Those participants reporting having RA or an FDR with RA were then invited in the second stage to take the full survey which included the DCE. Questions were included in the survey to better ascertain whether the respondent or their FDR had RA. The questions that identify those who with RA, were the questions "Do you have a physician-confirmed diagnosis of rheumatoid arthritis?" and "Are you currently taking, or have you previously been taking, a drug to treat rheumatoid arthritis, for example, methotrexate or a biologic drug?". To ensure that the patient group was accurately identified, only those who both reported having physician confirmed RA and currently/previously taking medications for RA were included in the patient group. Those that did not belong to this group, but reported having a FDR with RA or RA but not currently/previously taking medications for RA were classified as a first-degree relative (high-risk for RA).

Each respondent received a small payment (approximately $2) for completing the survey.
In the DCE survey (**Figure 3-1**), respondents completed 9 choice tasks in which they first chose between two preventative treatment options. Following this, respondents were then asked to choose between their preferred choice and no treatment (opt-out). Before starting the survey, respondents were provided background information around the symptoms and complications of RA, predictors of who will get RA, and potential preventative treatments for rheumatoid arthritis. Following this background information, video and text instructions were provided to describe

how to complete the DCE. Before each choice task, a background scenario was provided describing the risk of developing RA within the next 5 years and probability that the test to predict RA would be inaccurate. The DCE contained 5 attributes, each with 3 levels, giving 243 possible preventative treatment profiles and 29403 possible combinations of two-alternative choice questions. To generate a manageable set of choices for each participant, an experimental design was generated in collaboration with a statistician (Tima Mohammadi) using SAS. It is necessary for the number of combinations selected in each choice set to be at least be equal to or greater than the number of parameters estimated in the model (77). Having fewer combinations than this can lead to confounding around attributes causing them indistinguishable from each other (77). Therefore, to prevent confounding around attributes, 18 choice sets were blocked into 4 sets of 9 choices. The design of the DCE ensured that the principles of orthogonality (levels of each attribute vary independently of each other), level balance (all levels of each attribute to appear with equal frequency across choice sets) and minimum overlap (low probability of a repeated attribute level) were incorporated. There are formal sample size calculations for DCEs (101), however they require an initial estimate of what the coefficients for each of the attribute levels would be. Since the coefficients around each attribute level are not known, I was not able to do a formal sample size calculation. Therefore, based on that robust choice models have been estimated from sample sizes between 50 to 100 (93), I assumed that a minimum of 50 responses for each choice set would be sufficient and allow for the exploration of heterogeneity in preferences between respondents.

Figure 3-1: Example Choice Set in the Discrete Choice Experiment



Imagine that you have taken a test to predict your risk of developing rheumatoid arthritis (RA), and these are the results:

- **Risk of developing rheumatoid arthritis** in the next 5 years: 60% (60 out of 100 people like you are expected to develop RA)
- **Chance that the test is wrong**: 20% (20 out of 100 people are expected to get inaccurate information from this test)

Imagine you are now offered the choice between two treatments which could prevent you developing rheumatoid arthritis. Both are thought to be appropriate, but differ in a number of ways.

Part 1: choose your **preferred treatment.**

Click here if you are unsure what to do.

	Treatment A	Treatment B
Your risk of developing rheumatoid arthritis	Your predicted risk of RA would reduce from *60 people out of 100* to *44 people out of 100* over the next 5 years.	Your predicted risk of RA would reduce from *60 people out of 100* to *24 people out of 100* over the next 5 years.
The way you take the treatment	*IV/slow drip*, given by a physician or nurse at their office or hospital, which takes 3-4 hours / *Twice, 15 days apart, repeated once (2 doses total)*.	An *oral pill* / *Once daily* for one year.
Chance of side effects	Common: minor side effect which is *reversible* Very rare: very serious side effect which is *not reversible*.	Common: minor side effect which is *reversible*
Certainty in estimates	Very little: The true effect is *likely to be substantially different* from the estimate of effect.	Limited: The true effect *may be substantially different* from the estimate of the effect.
Your health care provider's opinion	Your health care provider would *not prefer* this treatment.	Your health care provider would *prefer* this treatment.
I prefer:	○	○

Part 2: Would you choose **no treatment for now**, over your chosen treatment above?

	No treatment
Your risk of developing rheumatoid arthritis	Your predicted risk will stay the same at *60 people out of 100*.
The way you take the treatment	You don't take anything
Chance of side effects	None
Certainty in estimates	High: The true effect is *likely to be close* to the estimate of the effect.
Your health care provider's opinion	Your health care provider *does not offer an opinion* about this option.

I choose to:

○ Stay with selected treatment
○ Choose no treatment

3.2.3 Data Analysis

The characteristics and other descriptive information about participants who filled questionnaires were summarized using descriptive statistics. Only those who completed the DCE and responded to having either a first degree relative with RA and having RA were included in the analysis. Respondents that did not complete the DCE, who did not report having either a first degree relative with RA or having RA were excluded from the analysis. A previous DCE(81) similar in length excluded those who completed the entire survey in less than 3 minutes, I tested the time that it took our respondents to complete the DCE, and excluded any respondent completing DCE in less than 3 minutes.

The DCE responses were analyzed in 3 stages. Stage 1 used a conditional logit model (103) on the forced choice component of the questions they completed (i.e. treatment A versus treatment B), ignoring, at this stage, the opt-out component. The aim of this stage of the analysis was to understand the trade-offs people make between different treatments. The conditional logit model assumes that the utility function can be defined by levels of each attribute. Initially to assess the direction of model co-efficients, these forced choice DCE responses were analyzed using dummy coding for the attribute levels assigning the reference group to the expected least preferable level of each attribute. Following this, a conditional logit model was used with effects coded attribute levels of this forced choice data (**Table 3-2**) to explore trade-offs between attributes, to allow for the coefficients all attribute levels to be estimated and for coefficients to be estimated relative to the mean attribute effect. Effects coding uses 0 or 1 to represent the presence or absence of an attribute level with the exception for when the reference group is present. To obtain the reference

level coefficient for each attribute, the coeffiecients for the non-reference levels were multiplied by negative one then summed.

Table 3-2: Example of Effects Coding Scheme in DCE Design

ID	Treatment Pair	Treatment Number	Risk Reduction from 66 to 34	Risk Reduction from 66 to 24	Injection	Tablet	3 Remaining attributes…	Forced Choice	Opt Out
1	9	1	1	0	-1	-1	⋯	0	0
1	9	2	-1	-1	1	0	⋯	1	0
1	9	3	0	0	0	0	⋯		1
2	2	1	0	1	0	1	⋯	1	1
2	2	2	-1	-1	-1	-1	⋯	0	0
2	2	3	0	0	0	0	⋯		0

When the reference group is present, each of the attribute levels that are not omitted are set to -1. For example, in **Table 3-2**, for respondent (ID) 1, treatment pair 9, and treatment number 1, the treatment seen by the respondent would be risk reduction of RA from 66 to 34 (indicated by the presence of a 1 for the risk reduction of RA from 66 to 34 and 0 for the risk reduction of RA from 66 to 24 in the attribute levels) and infusion (the reference group is indicated by the presence of a -1 for both the non-omitted injection and tablet attribute levels). For the forced choice models, choice that is modelled is shown in the 'Forced Choice' column of Table 3-2, and predicted, conditional on the attributes shown for each pair, for example out of the pair of treatments number 9, treatment 2 was chosen (denoted by a 1 in the Forced choice column).

Marginal rates of substitution were calculated by scaling all attributes and their levels terms of the largest available risk reduction of RA (an absolute risk reduction of 36, risk of RA of 60 reduced to 24). The largest available risk reduction of RA was calculated using the coefficient for risk reduction of RA modelled as a continuous variable, multiplied by 36. The coefficients within each attribute level were divided by this largest available risk reduction of RA. The

obtained value for each attribute level was then rescaled into percentage points of risk reduction that would be traded to have each attribute level by dividing by it by the coefficient per unit of risk reduction of RA modelled as a continuous variable.

Stage 2 sought to consider heterogeneity in individual preferences and using individual preference to predict which of the current treatments under study in RCTs might be the preferred treatment of respondents (**Table 3-3**). To estimate individual preferences a mixed logit model was used, again with the forced choice portion of the DCE. The mixed logit model assumes that the probability of choosing a treatment from a set of alternatives is a function of the attribute levels that describe the alternatives and a random error that adjusts for individual-specific variations in preferences. A post-estimation command in STATA (mixlbeta) was then used to obtain individual specific parameters that represented individual preferences for different attribute levels to be estimated. These individual specific coefficients were used predict which of the current treatments might be their preferred option (i.e. which treatment, when described using the attribute levels within my DCE, has the highest utility value utility for that individual). For example, for oral methotrexate the coefficients that describe the treatment (i.e. risk reduction of RA from 66 to 34, for oral administration, major and minor reversible side effects, limited certainty in estimates, health care provider prefers) would be summed for each individual. Preferred treatment for each individual was defined as the treatment offering the greatest overall utility (highest sum). These individual specific coefficients for each treatment were averaged and their 95% confidence intervals calculated to understand differences between the predicted utilities for each treatment.

Table 3-3: Attributes and Levels of Current Preventative Treatments Under Study

	MTX*	HCQ	Abatacept*	Rituximab	Steroids*	Statins
Risk reduction of RA						
From 60 to 44 in 100		**X**				**X**
From 60 to 34 in 100	**X**				**X**	
From 60 to 24 in 100			**X**	**X**		
Method of Administration						
Infusion			**X**	**X**		
Injection	**X**		**X**		**X**	
Oral	**X**	**X**			**X**	**X**
Side Effects						
Minor reversible, major irreversible				**X**		
Minor reversible, major reversible	**X**		**X**			
Minor reversible		**X**			**X**	**X**
Certainty in Estimates						
Very little			**X**	**X**	**X**	
Limited	**X**	**X**				**X**
Moderate						
Preference of Health Care Provider						
Health Care Provider does not prefer			**X**	**X**	**X**	
Health Care Provider is indifferent						**X**
Health Care Provider prefers	**X**	**X**				

*Treatments have more than one method of administration

Levels based on discussions with Dr. Marie Hudson and Dr. Kam Shojania

Stage 3 sought to estimate the predicted uptake of the potential preventative treatments currently under study. This stage of analysis used the information from the opt-out portion of the DCE. The analysis took the form of a binary choice analysis. The outcome (choice) variable for this analysis is based on responses to the forced choice question and the opt out question. For example, in **Table 3-4**, respondent 1 chose treatment 2 (denoted by a 1 in the forced choice column) out of the two options presented in pair 9. This line of data relating to the chosen treatment (in this case treatment 2) becomes the line that will be analyzed in the binary choice analysis. If the respondent decides the opt out of 'no treatment for now' (denoted by a 0 in the opt out column) rather than treatment, then the treatment choice in the binary analysis is denoted by a 0 in the binary choice column. If the respondent, like individual 2 chooses treatment 1 and then chooses to remain on treatment 1 rather than to opt out, then this line of data is analyzed and the choice is denoted by a 0 in the binary choice column.

A logit model with random effects to account for the repeated observations within individuals was used to analyze the binary choice data. The coefficients for each attribute level were used to predict uptake of each preventative treatment, first versus no preventative treatment, and then against all other available options. To determine the uptake of each preventative treatment option, the coefficient of each attributes levels describing the treatment and logit constant were first summed. The exponential of this sum was then divided by the sum of the exponential of the sum of the preventative treatment option and no treatment. Multiplying the result by 100 gives the percent uptake of each preventative treatment option compared to only no treatment. To compare uptake of a preventative treatment to all other preventative treatments (including no treatment), the preventative treatments exponential sum was divided by the exponential sum of

all the preventative treatment options, which included no treatment. Multiplying this number by 100 gives the percent uptake of each preventative treatment option compared to all preventative treatment options (including no treatment). When determining both uptake compared to no and all preventative treatments, the coefficients describing no treatment were assumed to be 0. Attribute levels for each of the proposed preventative treatments (**Table 3-3**) were identified by a rheumatologist (Dr. Marie Hudson and Dr. Kam Shojania). In a sensitivity analysis, I allowed some of these treatment levels to vary to understand the extent to which predicted uptake of and preferences around preventative treatments depends on the levels selected.

In a sensitivity analysis of the mixed logit and conditional logit results, I allowed some of these treatment levels to vary to understand the extent to which predicted uptake of and preferences around preventative treatments depended on the levels selected. In the sensitivity analysis, I modified some of the attribute levels that described treatments to understand whether treatment preferences or uptake would change. These modifications around the attribute levels that described potential preventative treatments included changing the risk reduction of RA from 44 to 34 in 100 for hydroxychloroquine, health care provider from prefers to indifferent for methotrexate, the side effects for hydroxychloroquine from minor reversible to minor and major reversible, the side effects for methotrexate from minor and major reversible to minor reversible and major irreversible, and the attribute levels for health care provider preference to health care provider indifferent to all treatments. A chi-squared test was used to determine whether there were any statistically significant differences between RA patients, and first degree relatives predicted preferred preventative treatments. A chi-squared test is used on categorical data to test

the likelihood that any observed difference between the groups occurred by chance alone (the null hypothesis).

Table 3-4: Example of Binary Choice Scheme in DCE Design

ID	Treatment Pair	Treatment Number	5 Attributes	Force Choice	Opt Out	Binary Choice
1	9	1	…	0	0	
1	9	2	…	1	0	1
1	9	3	…		1	
2	2	1	…	1	1	0
2	2	2	…	0	0	
2	2	3	…		0	

3.3 Results

3.3.1 Characteristics of respondents

594 individuals completed the survey and were considered eligible for the analysis. No individual completed the survey in less than 4 minutes, well in excess of a cut-off of 3 minutes, therefore no one was excluded on the basis of completing the survey too quickly. **Table 3-5** summarizes the characteristics of individuals that were included in the analysis. The majority (96%) of respondents were between the ages of 25-64, from 25-39 age group (52%), female (59%), and from the United States (88%). Most respondents reported household income between $30,000 and $80,000 (54%), 20% reported household income below $30,000, 22% reported household income above $80,000 and 4% preferred not to report.

In this sample, 90% (n=535) reported having a family member with RA, 25% (n=151) reported a physician confirmed RA diagnosis and 16% (n=94) reported both. 20% (n=117) reported previously or currently taking medication such as methotrexate or a biologic to treat RA. Of the

151 individuals who reported physician confirmed RA, 109 (72%) reported previously or currently taking medication for RA. These 109 respondents were classified as the RA patient group in the analysis of the DCE. 30 (71%) of the 42 self-reported RA patients that did not report having taken a medication for RA reported having a first-degree relative with RA. All 42 of the self-reported RA patients were included in the first-degree relatives groups since they either had a first-degree relative with RA or they potentially could have confused rheumatoid arthritis with another type arthritis they might have such as osteoarthritis which would make them a higher risk of RA. The first-degree relatives group was classified as the remaining 485 individuals that did not report both physician confirmed RA and previously or currently taking medication for RA.

Table 3-5: Descriptive Table of DCE Respondent Characteristics (n=594)

Category	**RA Patients (N=109)**	**First-Degree Relatives (N=485)**	**All Respondents (N=594)**
Age			
18-24	<1% (1)	7% (36)	6% (37)
25-39	27% (29)	57% (278)	52% (307)
40-64	57% (62)	33% (158)	37% (220)
65+	15% (16)	3% (13)	5% (29)
Prefer not to say	<1% (1)	0% (0)	<1% (1)
Sex			
Male	70% (76)	42% (204)	40% (237)
Female	30% (33)	57% (278)	59% (354)
Other	0 (0%)	<1% (2)	<1% (2)
Prefer not to say	0 (0%)	<1% (1)	<1% (1)

Category	RA Patients (N=109)	First-Degree Relatives (N=485)	All Respondents (N=594)
Country			
Canada	46% (50)	4% (19)	11% (69)
USA	54% (59)	96% (466)	88% (525)
Household Income			
<$15,000	3% (3)	7% (35)	6% (38)
$15,000-$30,000	11% (12)	14% (68)	14% (80)
$30,000-$50,000	23% (25)	26% (127)	26% (152)
$50,000-$80,000	31% (34)	27% (130)	28% (164)
$80,000-$150,000	14% (15)	18% (88)	17% (103)
>$150,000	7% (8)	5% (23)	5% (31)
Prefer not to say	11% (12)	3% (14)	4% (26)
Physician Confirmed RA			
Yes	100% (109)	9% (42)	25% (151)
No	0% (0)	87% (424)	71% (423)
Unsure	0% (0)	4% (19)	4% (19)
Previously or Currently Taking Medication for RA			
Yes	100% (109)	2% (8)	20% (117)
No	0% (0)	96% (466)	79% (466)
Unsure	0% (0)	2% (8)	1% (8)
No Response	0% (0)	<1% (3)	<1% (3)

Category	RA Patients (N=109)	First-Degree Relatives (N=485)	All Respondents (N=594)
Family Member with RA			
Yes	59% (64)	97% (471)	90% (535)
No	32% (35)	2% (9)	7% (44)
Not Sure	9% (10)	1% (5)	3% (15)

3.3.2 Trade-offs between Treatments

The results from the forced choice conditional logit model with dummy coded attributes suggested that within each attribute all coefficients were logically ordered; levels of the attributes that were expected to be more favorable had positive coefficients indicating a preference for that level (e.g. Method of Administration: Oral (compared with the reference category of infusion). Respondents appeared to have the strongest preference for treatments that had minor reversible side effects, their health care provider preferred, had a large risk reduction of RA, moderate certainty in estimates and oral administration. Coefficients for the risk of side effects were similar for 'minor reversible' and 'minor and serious reversible' levels suggesting that potentially there may be aversion to irreversible side-effects rather than the severity or frequency of side effect. A summary of the coefficients for the forced choice dummy coded conditional logit can be found and effects coded conditional logit in **Table 3-6** and **Table A.1** in the appendix.

Table 3-6: Forced Choice Conditional Logit Model with Dummy Coding

	Coefficient	z	P
Risk of RA			
44	Reference		
34	0.459	10.02	<0.001
24	0.840	17.22	<0.001
Route of administration			
Infusion	Reference		
Injection	0.230	5.06	<0.001
Oral	0.977	20.41	<0.001
Side Effect			
Minor reversible, Serious irreversible	Reference		
Minor reversible, Serious reversible	0.828	17.74	<0.001
Minor reversible	0.867	17.77	<0.001
Certainty in Estimates			
Very little	Reference		
Limited	0.137	2.87	0.004
Moderate	0.481	10.42	<0.001
Preference of Health Care Provider			
Health care provider does not prefer	Reference		
Indifferent	0.493	11.09	<0.001
Health care provider prefers	0.869	18.71	<0.001
No. of responses	10692		
No. of respondents	594		
Log-likelihood	-2907.13		

Table 3-7 reports the marginal rate of substitution for the levels of each attribute in the DCE. These are presented as the percentage of the absolute risk reduction of RA that respondents, on average would be willing to give up (or accept as compensation) for each attribute. These results, presented on a common scale, show that respondents would be most willing to trade for the method of administration of treatment followed by the side effects. Respondents were willing to trade the greatest absolute risk reduction of RA for a daily oral administration of treatment (willing to give up 9% of the risk reduction for a daily oral treatment, 95% CI 8.2% to 9.9%).

In contrast, to accept treatments that had serious irreversible side effects alongside minor reversible side effects, or to accept a treatment administered by infusions, respondents would require the treatment to offer an additional 9% and 6% increase in the absolute risk reduction of RA respectively.

To have a treatment that matched the preference of their health care provider, respondents would, on average, be willing to trade 7% of the risk reduction available (95% CI 5.8% to 7.4%). Respondents were least willing to give up (or accept) the least amount of absolute RA risk reduction to improve certainty in estimates, willing to trade only 4% of the available reduction in the risk of developing RA for treatments that had moderate certainty in estimates whilst only needing to an additional 3% increase in risk reduction of RA to compensate for the treatments having very little certainty in estimates.

Table 3-7: Marginal Rates of Substitution of Absolute Risk Reduction of RA by Attribute

	Percent	95% Lower CI	95% Upper CI
Route of administration			
Infusion	6.3	4.7	8.0
Injection	2.7	1.9	3.5
Oral	-9.0	-8.2	-9.9
Side Effect			
Minor reversible, Serious irreversible	8.9	7.2	10.5
Minor reversible, Serious reversible	-4.1	-3.3	-4.9
Minor reversible	-4.7	-3.9	-5.6
Certainty in Estimates			
Very little	3.3	1.6	4.8
Limited	1.1	0.3	1.9
Moderate	-4.3	-3.5	-5.1
Health Care Provider Preference			
Health care provider does not prefer	7.1	5.6	8.8
Indifferent	-0.6	-1.4	0.2
Health care provider prefers	-6.5	-5.8	-7.4

3.3.3 Predicting Preferred Preventative Treatments

A mixed logit model was used to estimate individual coefficients for the strength of preferences for each person in my sample. To predict that treatment that would be preferred by each individual in my sample, I estimated the expected utility of each treatment in **Table 3-3**, by adding the individual coefficients that describe each treatment. For example, for oral methotrexate the coefficients that describe the treatment (i.e. risk reduction of RA from 66 to 34, for oral administration, major and minor reversible side effects, limited certainty in estimates,

health care provider prefers) would be summed for each individual. Preferred treatment for each individual was the treatment offering the greatest utility (highest sum).

The treatment that was predicted to be the preferred treatment for the majority of respondents was oral methotrexate (70%) followed by hydroxychloroquine (20%) (**Table 3-8**). There were few respondents (8%) who were predicted to prefer the biologic drugs abatacept or rituximab as preventative treatments.

Table 3-8: Prediction of Preferred Preventative Treatment

Treatment	Predicted Preferred Treatment
Oral MTX	414 (70%)
Injectable MTX	5 (<1%)
Hydroxychloroquine	118 (20%)
Infused ABA	34 (6%)
Injectable ABA	4 (<1%)
Infused RTX	2 (<1%)
Injected steroid	0 (0%)
Oral steroid	13 (2%)
Statin	4 (<1%)

In those for whom oral methotrexate was predicted to be the preferred treatment, hydroxychloroquine (67%) was most frequently predicted to be their second preferred treatment (**Table 3-9**). This suggests that if oral methotrexate was not offered as a preferred treatment, 66% of respondents (number of individuals who preferred hydroxychloroquine as their first choice treatment (n=118) and as their second choice treatment (n=273) divided by number of respondents (n=594)) would be predicted to prefer hydroxychloroquine as their first choice.

Table 3-9: Prediction of 2nd Preferred Preventative Treatment of Those Who Preferred Methotrexate (n=414)

Treatment	Predicted Preferred Treatment
Oral MTX	X
Injectable MTX	63 (15%)
Hydroxychloroquine	273 (66%)
Infused ABA	32 (8%)
Injectable ABA	8 (2%)
Infused RTX	0 (0%)
Injected steroid	0 (0%)
Oral steroid	36 (9%)
Statin	2 (<1%)

Comparing the predicted individual mean utilities for each of the treatments (with 95% confidence intervals) in **Figure 3-2** for all respondents, **Figure 3-3** for RA patients, and **Figure 3-4** for first-degree relatives highlights the fact that although oral methotrexate is predicted to be the most preferred treatment, the estimated utility of this treatment is only slightly higher than for hydroxychloroquine. This indicates that the definition of 'preferred treatment' may be skewed toward oral methotrexate when the actual difference in predicted preference between oral methotrexate and hydroxychloroquine may be negligible. The mean utilities for oral treatments were generally higher compared to treatments given either as injections or infusions.

Figure 3-2: Estimated Mean Individual Utility For Each Preventative Treatment

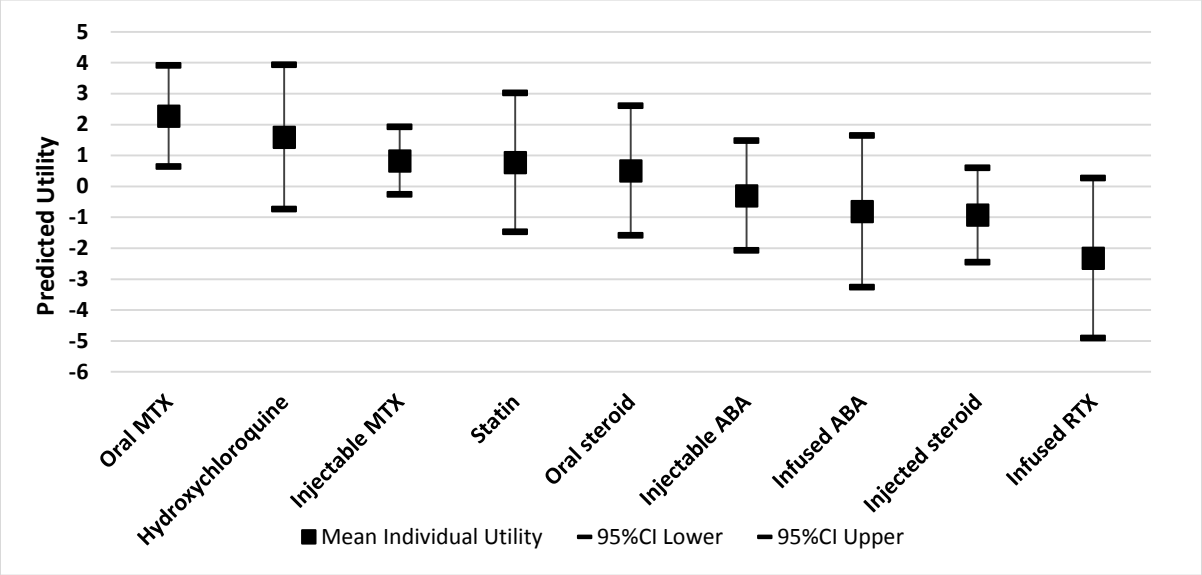


Figure 3-3: Estimated Mean Individual Utility For Each Preventative Treatment For RA Patients

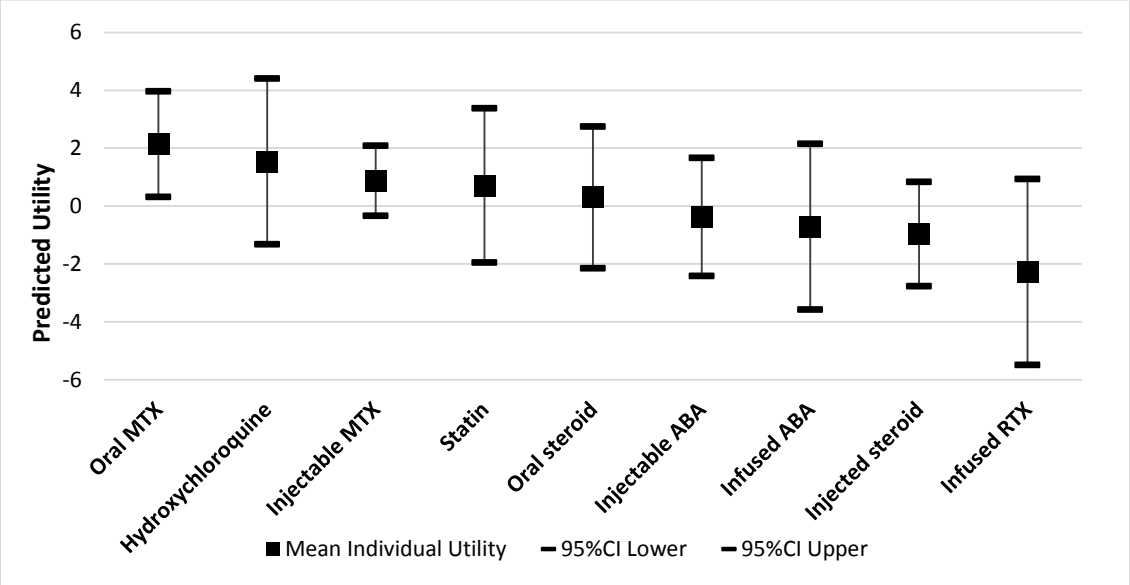
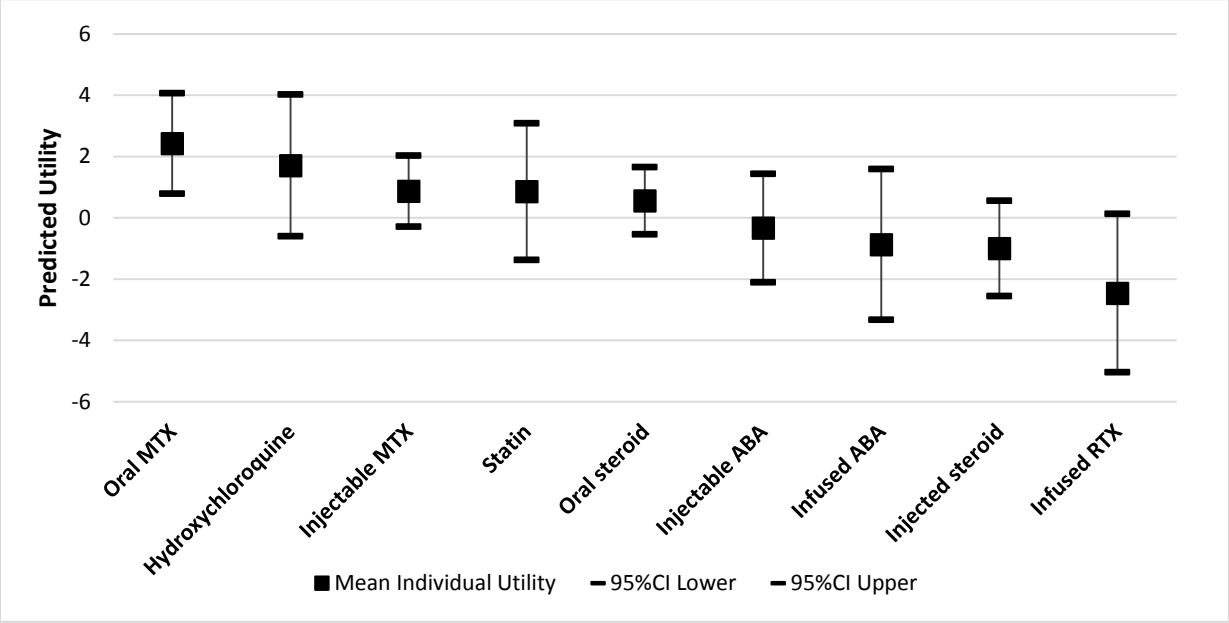


Figure 3-4: Estimated Mean Individual Utility For Each Preventative Treatment For First Degree Relatives



Comparing preferred treatment in RA patients and their first-degree relatives, oral methotrexate was still preferred over any of the other proposed preventative treatments in 72% of first-degree relatives and 60% of RA patients. Following methotrexate, hydroxychloroquine was the second most preferred treatment in both groups (19% of first-degree relatives, 23% of RA patients). A larger proportion of first-degree relative preferred any of the oral treatments compared to RA patients (94% vs. 87%). Examining preferences for treatments that are currently used to treat RA (oral methotrexate and hydroxychloroquine), 91% of first-degree relatives preferred either treatment compared to around 84% of RA patients. Any infused drug was preferred by a larger proportion of RA patients than first-degree relatives (12% vs. 6%). There were no statistically significant differences in predicted preferred treatment between patients and first-degree relatives (Chi-Squared = 12.75, p-value =0.079) (**Table 3-10**).

Table 3-10: Prediction of Preventative Treatment Preferred by First-Degree Relatives and Patients

Preferred Treatment	First-Degree Relatives	RA Patients*	Total
Oral MTX	348(72%)	66 (61%)	414 (70%)
Injectable MTX	3 (1%)	2 (2%)	5 (1%)
Hydroxychloroquine	93 (19%)	25 (23%)	118 (20%)
Infused ABA	22 (5%)	12 (11%)	34 (6%)
Injectable ABA	4 (1%)	0 (0%)	4 (1%)
Infused RTX	1 (<1%)	1 (1%)	2 (<1%)
Injected steroid	0 (0%)	0 (0%)	0 (0%)
Oral steroid	11 (2%)	2 (2%)	13 (2%)
Statin	3 (1%)	1 (1%)	4 (1%)
Total	485	109	594
Chi-Squared = 12.75, p-value =0.079			

Restricting predicted preferences of preventative treatments to those that are currently under study in clinical trials (**Table 3-11**) showed that the majority of respondents (81%) might be expected to prefer hydroxychloroquine. Hydroxychloroquine was predicted to be the preferred treatment with 82% of first-degree relatives and 76% of RA patients followed by infusion abatacept (12% in first-degree relatives; 19% in RA patients). There were no statistically significant differences in predicted preferred treatment between patients and first-degree relatives (Chi-Squared = 5.22, p-value =0.156).

Table 3-11: Prediction of Preventative Treatments Currently Studied Preferred by First-Degree Relatives and Patients

Preferred Treatment	First-Degree Relatives	RA Patients*	Total
Hydroxychloroquine	396 (82%)	83 (76%)	479 (81%)
Infused ABA	56 (12%)	21 (19%)	77 (13%)
Injectable ABA	32 (7%)	5 (5%)	36 (6%)
Infused RTX	1 (<1%)	0 (0%)	2 (<1%)
Total	485	109	594
Chi-Squared = 5.22, p-value =0.156			

3.3.4 Sensitivity Analysis Around Preferred Choice of Preventative Treatment

Varying the attribute levels that described each of the possible preventative treatment programs, methotrexate who was preferred treatment when health care providers were indifferent to any of the proposed preventative treatments or hydroxychloroquine and methotrexate.

Hydroxychloroquine became the preferred treatment if the preference of health care providers for methotrexate was changed from preferred to indifferent (55% of people predicted to prefer hydroxychloroquine versus 29% for oral methotrexate), when methotrexate and hydroxychloroquine were expected to provide the same magnitude of risk reduction of RA (64% of people predicted to prefer hydroxychloroquine compared to 28% for oral methotrexate), and when methotrexate was described as having a major irreversible side effects instead of reversible minor side effects (60% of people predicted to prefer hydroxychloroquine versus 19% for oral methotrexate). A summary of the predicted preferred treatments in the scenarios where hydroxychloroquine was preferred can be found in **Tables 3-12 to 3-14**.

Only when methotrexate and hydroxychloroquine were expected to provide the same magnitude of risk reduction of RA there were significant differences in preferred treatments between first-degree relatives and RA patients (Chi-Squared= 14.79, P-value =0.039). These differences appear to be driven primarily by a greater proportion of RA patients preferring abatacept infusion compared to first-degree relatives (11% vs 4%).

Table 3-12: Predicted Preference for Preventative Treatment in First-Degree Relatives and Patients Adjusting Risk Reduction of RA from 44 to 34 in 100 for Hydroxychloroquine

Preferred Treatment	**First-Degree Relative**	**RA Patient**	**Total**
Oral MTX	140 (28.0%)	29 (26.6%)	165 (27.8%)
Injectable MTX	2 (0.4%)	2 (1.8%)	4 (0.7%)
Hydroxychloroquine	312 (64.3%)	61 (60.0%)	373 (62.8%)
Infused ABA	19 (3.9%)	12 (11.0%)	31 (5.2%)
Injectable ABA	3 (0.6%)	0 (0%)	3 (0.5%)
Infused RTX	1 (0.2%)	1 (0.9%)	2 (0.3%)
Injected steroid	0 (0%)	0 (0%)	0 (0%)
Oral steroid	3 (0.6%)	1 (0.9%)	4 (0.7%)
Statin	9 (1.9%)	3 (2.8%)	12 (2.0%)
Total	485	109	594
Chi-Squared= 14.79, P-value =0.039			

Table 3-13: Predicted Preference for Preventative Treatment in First-Degree Relatives and Patients Adjusting Health Care Provider to Indifferent for Methotrexate

Preferred Treatment	First-Degree Relative	RA Patient	Total
Oral MTX	142 (29.3%)	25 (22.9%)	167 (28.1%)
Injectable MTX	2 (0.4%)	0 (0%)	2 (0.3%)
Hydroxychloroquine	265 (54.6%)	60 (55.1%)	325 (54.7%)
Infused ABA	52 (10.7%)	17 (15.6%)	69 (11.6%)
Injectable ABA	6 (1.2%)	2 (1.8%)	8 (1.4%)
Infused RTX	1 (0.2%)	1 (0.9%)	2 (0.3%)
Injected steroid	0 (0%)	0 (0%)	0 (0%)
Oral steroid	14 (2.9%)	4 (3.7%)	18 (3.0%)
Statin	3 (0.6%)	0 (0%)	3 (0.5%)
Total	485	109	594
Chi-Squared= 5.97, P-value =0.540			

Table 3-14: Predicted Preference for Preventative Treatment in First-Degree Relatives and Patients Adjusting Methotrexate to Major Irreversible and Minor Reversible Side Effect

Preferred Treatment	First-Degree Relative	RA Patient	Total
Oral MTX	94 (19.4%)	12 (11.0%)	106 (17.9%)
Injectable MTX	0 (0%)	0 (0%)	0 (0%)
Hydroxychloroquine	290 (59.8%)	66 (60.6%)	356 (59.9%)
Infused ABA	53 (10.9%)	20 (18.4%)	73 (12.3%)
Injectable ABA	9 (1.9%)	2 (1.8%)	11 (1.9%)
Infused RTX	1 (0.2%)	1 (0.9%)	2 (0.3%)
Injected steroid	0 (0%)	0 (0%)	0 (0%)
Oral steroid	34 (7.0%)	7 (6.4%)	41 (6.9%)
Statin	4 (0.8%)	1 (0.9%)	5 (0.8%)
Total	485	109	594
Chi-Squared= 8.883, P-value =0.180			

3.3.5 Trade-offs between Treatments When Allowing for Opt Out

The final set of analyses use data which allow the respondents to opt out of treatment for now, after first identifying their preferred treatment. The initial focus of this analysis is to consider the consistency of results on preferences for different attributes, once the opt out is allowed. The results from the logit model with random effects (**Table 3-15**) show that within each attribute all coefficients remained logically ordered; levels of the attributes that were more favorable had positive coefficients indicating a preference for that level (e.g. Method of Administration: Oral) supporting and validating the findings previously discussed in the forced choice scenario. As previously, results indicated that respondents had positive preferences for preventative

treatments that had a high risk reduction of RA (from 60 in 100 within 5 years to 24 in 100 within 5 years), oral administration, reversible minor side effects, moderate certainty in estimates of risks and benefits, and the preference of the health care provider. A summary of logit model with random effects for RA patients and first-degree relatives can be found in **Table 3-16** and **Table 3-17**.

Table 3-15: Coefficients of Dummy Coded Logit Model with Random Effects for Opt-Out

	Coefficient	z	P
Risk Reduction of RA			
From 66 to 44	Reference		
From 66 to 34	0.950	8.82	<0.001
From 66 to 24	1.455	12.64	<0.001
Route of administration			
Infusion	Reference		
Injection	-0.021	-0.17	.862
Oral	1.044	9.10	<0.001
Side Effect			
Minor Reversible, Serious Irreversible	Reference		
Minor reversible, Serious reversible	0.654	5.51	<0.001
Minor reversible	0.916	7.51	<0.001
Certainty in Estimates			
Very little	Reference		
Limited	0.242	2.18	0.030
Moderate	0.800	7.17	<0.001
Preference of Health Care Provider			
Health care provider does not prefer	Reference		
Indifferent	0.231	2.04	0.042
Health care provider prefers	0.988	8.60	<0.001
Constant	-1.418	-6.46	<0.001
No. of observations	5346		
No. of respondents	594		
Log-likelihood	-2405.68		

Table 3-16: Coefficients of Dummy Coded Logit Model with Random Effects for Opt-Out for First-Degree Relative

	Coefficient	z	P
Risk Reduction of RA			
From 66 to 44	Reference		
From 66 to 34	0.984	7.76	<0.001
From 66 to 24	1.575	12.23	<0.001
Route of administration			
Infusion	Reference		
Injection	-0.057	-0.42	0.671
Oral	1.286	9.87	<0.001
Side Effect			
Minor Reversible, Serious Irreversible	Reference		
Minor reversible, Serious reversible	0.661	4.94	<0.001
Minor reversible	0.922	6.75	<0.001
Certainty in Estimates			
Very little	Reference		
Limited	0.152	1.22	0.221
Moderate	0.837	6.73	<0.001
Preference of Health Care Provider			
Health care provider does not prefer	Reference		
Indifferent	0.326	2.57	0.010
Health care provider prefers	1.021	-7.12	<0.001
Constant	-1.780	-7.12	<0.001
No. of observations	4365		
No. of respondents	485		
Log-likelihood	-1961.4`		

Table 3-17: Coefficients of Dummy Coded Logit Model with Random Effects for Opt-Out for RA Patients

	Coefficient	z	P
Risk Reduction of RA			
From 66 to 44	Reference		
From 66 to 34	0.918	3.34	0.001
From 66 to 24	1.129	4.10	<0.001
Route of administration			
Infusion	Reference		
Injection	0.181	0.24	0.515
Oral	0.062	2.23	0.812
Side Effect			
Minor Reversible, Serious Irreversible	Reference		
Minor reversible, Serious reversible	0.601	2.23	0.026
Minor reversible	0.925	3.28	0.001
Certainty in Estimates			
Very little	Reference		
Limited	0.515	1.98	0.048
Moderate	0.630	2.35	0.019
Preference of Health Care Provider			
Health care provider does not prefer	Reference		
Indifferent	-0.108	-0.41	0.678
Health care provider prefers	1.068	3.92	<0.001
Constant	0.149	-0.31	0.758
No. of observations	981		
No. of respondents	109		
Log-likelihood	-414.56		

3.3.6 Predicting Uptake of Potential Preventative Treatments Using Opt-out

Across all respondents 67% of people indicated that they would take their preferred treatment compared with nothing for now, this varied by group; RA patients indicated that they would take their preferred treatment 76% of the time, while first degree relatives accepted their preferred treatment 66% of the time. The coefficients from each of the effects coded logit models with random effects (**Appendix A.2-A.4**) were used to predict the potential uptake of different preventative treatments for RA that have been suggested or are currently under study.

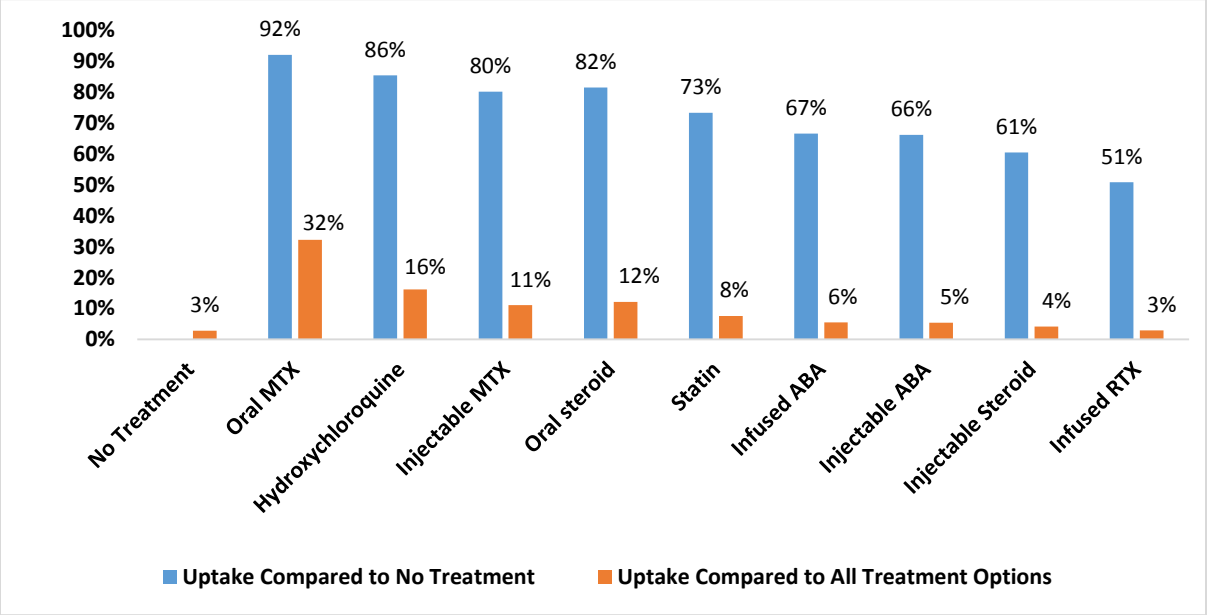
Comparing across all the model coefficients using an effects coded logit model with random effects (**Table A.2 in Appendix**), respondents attached the highest relative value to an oral method of administration followed by the risk reduction of RA from 66 to 24 in 100 over 5 years and treatment that was preferred by their health care provider. Respondents appeared to have the greatest aversion to small risk reductions of RA from 66 to 44 in 100 over 5 years, the possibility of having serious irreversible side effects alongside minor reversible side effects, treatments that their health care provider did not prefer, and having treatments with very little certainty in evidence.

RA patients attached the highest relative value to a treatment that was preferred by their health care provider, risk reduction of RA from 66 to 24 in 100 over 5 years, side effects that are minor and reversible, moderate level of evidence, and administration by injection (**Table A.3 in Appendix**). First-degree relatives attached the highest value to a treatment that an oral method of administration, risk reduction of RA from 66 to 24 in 100 over 5 years, that was preferred by

their health care provider, moderate level of evidence, and side effects that were minor and reversible (**Table A.4 in the Appendix**).

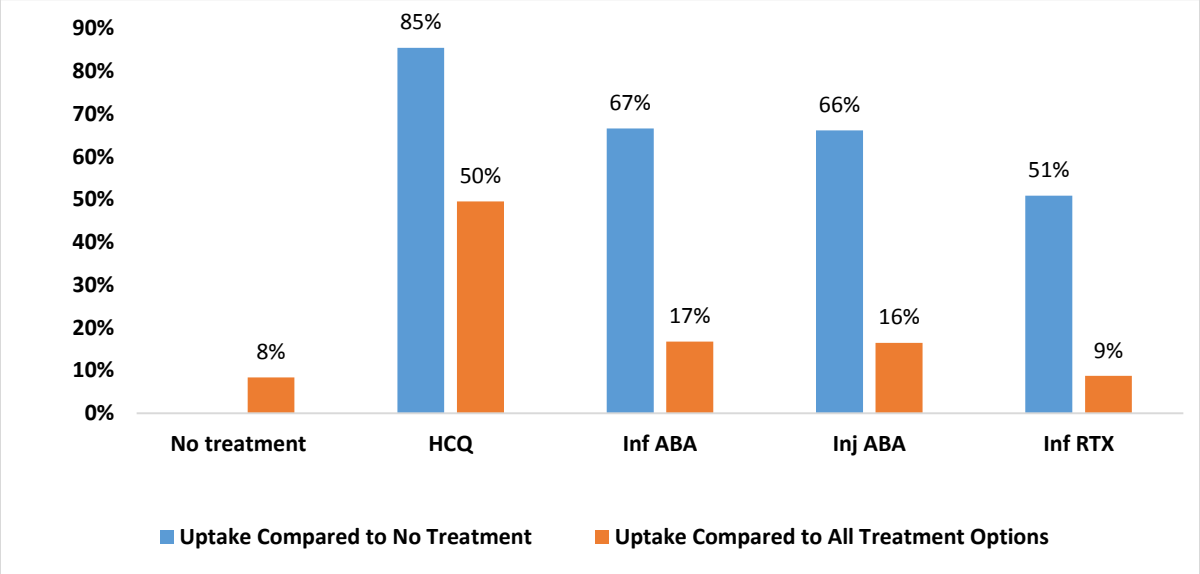
These estimated predicted uptake of each of the potential preventative treatment presented in **Figure 3-5** and **Appendix A.5**, indicate that oral methotrexate (92%) and hydroxychloroquine (86%) had the highest predicted uptake, if compared directly with no treatment. Infused rituximab had the lowest predicted uptake (51%) followed by injectable steroids (61%). In a situation when all other treatments were concurrently available, along with no treatment, the uptake of oral methotrexate was expected to be the highest of a treatments modelled (32%) followed by hydroxychloroquine (16%). In this scenario with multiple preventative treatment options available, the uptake of infused rituximab (3%) or injected steroids (4%) was very low. In a scenario with 9 potential treatments available, choosing 'no treatment for now' was expected to account for only 3% of options.

Figure 3-5: Prediction of Preventative Treatment Uptake and Preference in All Respondents



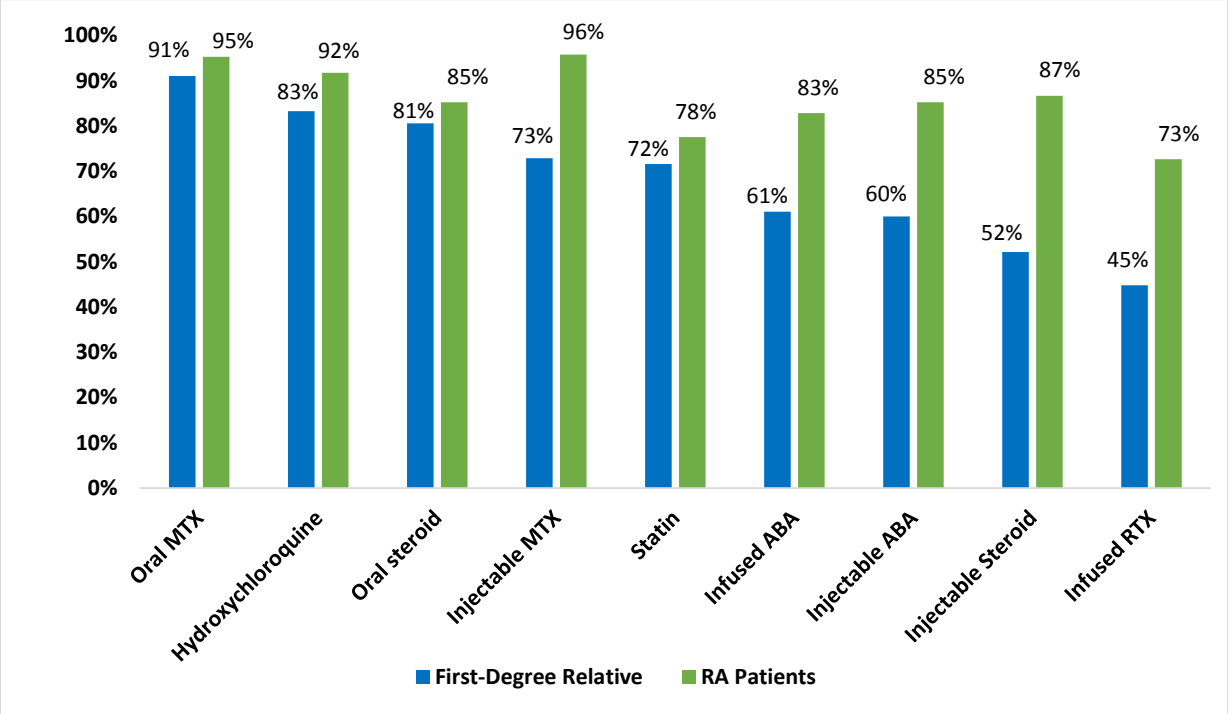
Considering only the preventative treatments that are currently in clinical trials (**Figure 3-6**), hydroxychloroquine was expected to have the highest uptake (85%) compared to no treatment, followed by infusion abatacept (67%). In a scenario with each of these potential treatments available, 50% of respondents would be expected to prefer hydroxychloroquine followed by infusion abatacept (17%). Choosing 'no treatment for now' was expected to account for only 8% of options.

Figure 3-6: Prediction of Preventative Uptake and Preference of Treatments Currently Under Study in All Respondents



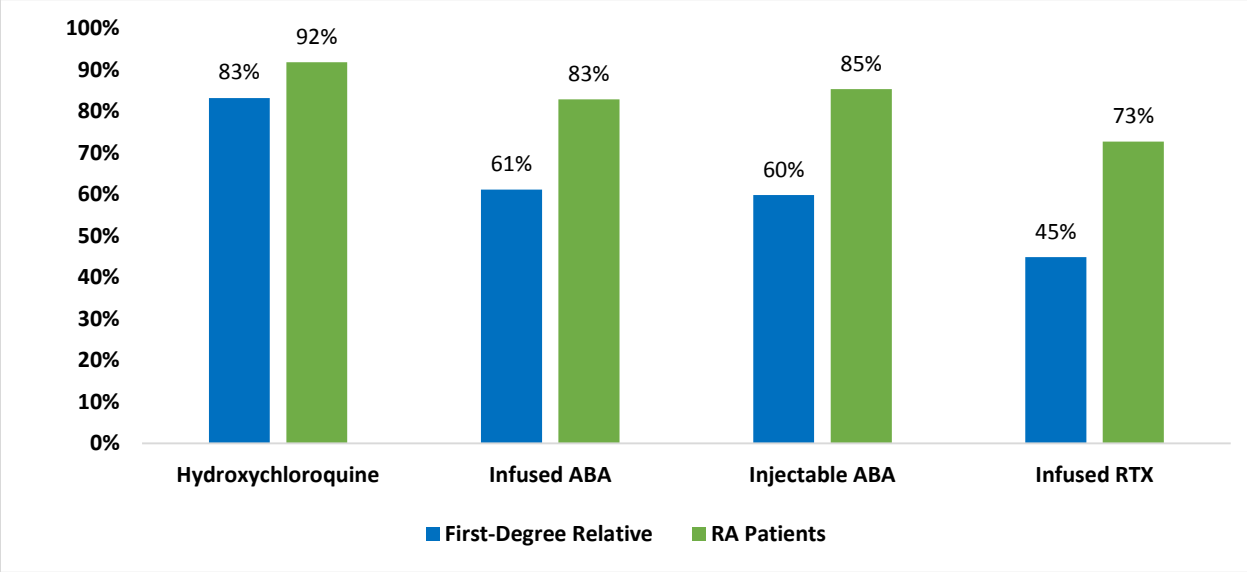
When the sample was split into RA patients and first-degree relatives, results suggested that all treatments had a higher probability of uptake (73% (infused rituximab) to 96% (injected methotrexate)) in the RA patient sample compared with first-degree relatives (45% (infused rituximab) to 91% (oral methotrexate)) relative to no treatment. Rituximab had the lowest predicted uptake in both groups, uptake was predicted to be 73% for RA patients and 45% for first-degree relatives. Uptake of oral methotrexate was predicted to be the highest in first-degree relatives followed by hydroxychloroquine. Predicted uptake of methotrexate was 95% for RA patients and 91% for first-degree relatives, and hydroxychloroquine was 92% for RA patients and 83% for first-degree relatives. A summary of predictions of preventative treatment uptake in first-degree relatives and RA patients can be found in **Figure 3-7** and in **Appendix A.6.**

Figure 3-7: Prediction of Preventative Treatment Uptake in First-Degree Relatives and RA Patients Relative to No Treatment



Considering only the preventative treatment options currently in clinical trials results suggested that all treatments had a higher probability of uptake (73% (infused rituximab) to 92% (hydroxychloroquine)) in the RA patient sample compared with first-degree relatives (45% (infused rituximab) to 83% (hydroxychloroquine)) relative to no treatment. Uptake of hydroxychloroquine was predicted to be the highest in first-degree relatives followed by infused abatacept. Predicted uptake of hydroxychloroquine was 92% for RA patients and 83% for first-degree relatives, and infused abatacept was 83% for RA patients and 61% for first-degree relatives. A summary of predictions of preventative treatment uptake in treatments currently in clinical trials for first-degree relatives and RA patients can be found in **Figure 3-8**.

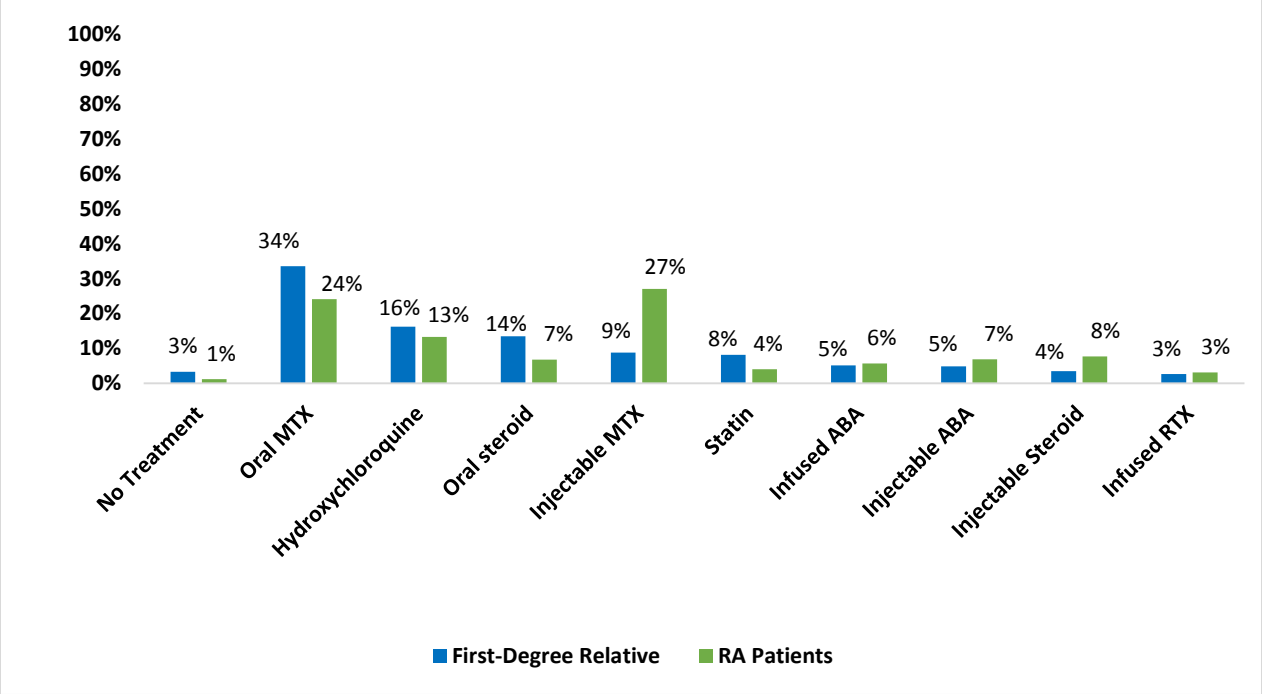
Figure 3-8: Prediction of Uptake in First-Degree Relatives and RA Patients of Treatments Currently Under Study Relative to No Treatment



Predicted preventative treatment uptake compared to all the available preventative treatment options varied between RA patients and first-degree relatives. Over 70% of first-degree relatives were predicted to prefer treatments were administered orally compared to about 50% of RA patients. The two oral treatments currently used in RA treatment oral methotrexate and hydroxychloroquine, had the highest predicted uptake for (34% and 16%) in first-degree relatives. Injectable (27%) and oral (24%) methotrexate had the highest predicted uptake for in RA patients compared to all treatments. About 50% of RA patients were predicted to prefer treatments that were non-oral, with 27% being predicted to prefer injectable methotrexate, 8% injectable steroids, and 7% injectable abatacept. This compared to about 30% of first-degree relatives being predicted to prefer non-oral treatments, with 9% being predicted to prefer injectable methotrexate, 7% injectable abatacept and 7% injectable steroids. Only 3% of first degree relatives and 1% of RA patients were predicted to prefer no treatment. A summary of

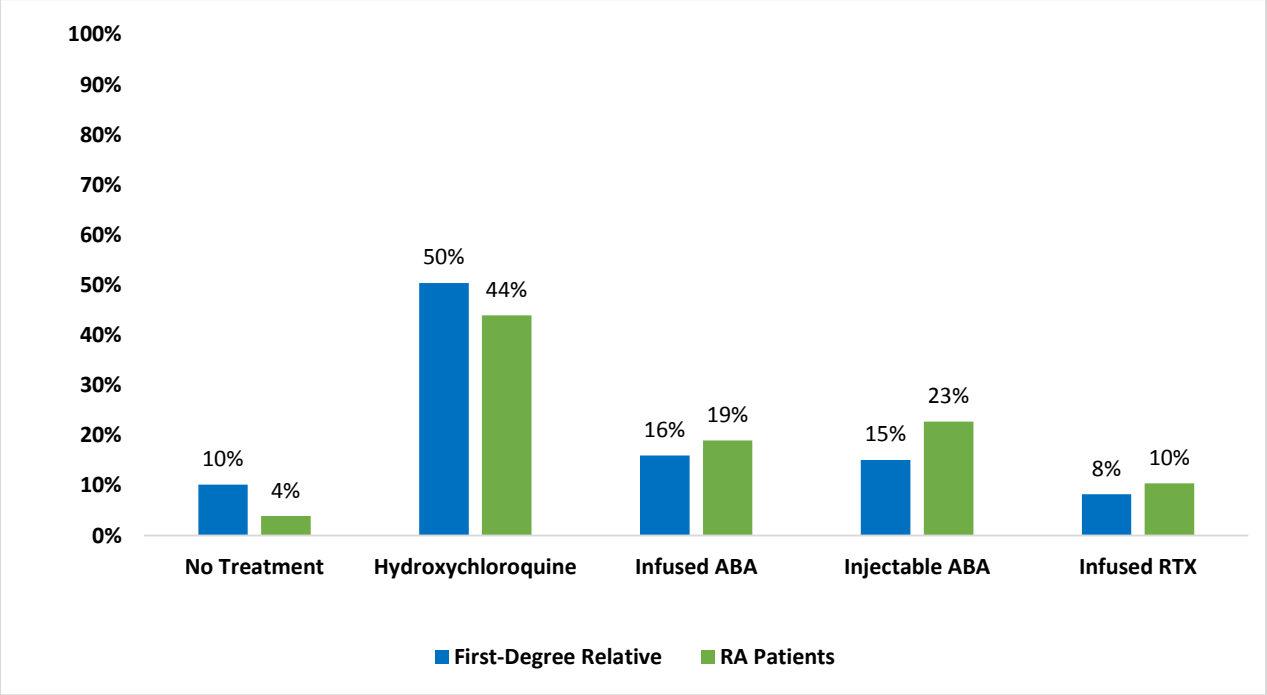
preventative treatment preferences in RA patients and first-degree relatives is provided in **Figure 3-9** and **Appendix A.7**.

Figure 3-9: Prediction of Uptake Compared to All Treatment Options in First-Degree Relatives and RA Patients



Predicted preventative treatment uptake compared to preventative treatment options currently in clinical trials (**Figure 3-10**) were similar between RA patients and first-degree relatives. Hydroxychloroquine was predicted to be preferred by 50% of first-degree relatives and 44% of RA patients. Treatment uptake of biologics was low ranging from 8% to 16% in first-degree relatives and 10% to 23% in RA patients. 10% first degree relatives preferred no treatment while compared to only 4% of RA patients.

Figure 3-10: Prediction of Uptake of Treatments Currently Under Study Compared to All Treatment Options in First-Degree Relatives and RA Patients



3.3.7 Sensitivity Analysis Around Predicting Preventative Treatments Preferences Using Opt-out

Predictions of uptake were very robust to changes in some assumptions around the levels that best represent the different treatments. Holding all other levels constant, assuming a greater reduction in the risk of developing RA from taking hydroxychloroquine increased the predicted uptake for this drug considerably, and it became drug with the highest predicted uptake relative to no treatment and compared any other treatment.

If either the health care provider preference for methotrexate was changed to indifferent (from a preferred treatment), or the side effects profile of methotrexate was increased from major reversible to major irreversible, the predicted uptake and methotrexate and hydroxychloroquine

became similar. Increasing the risk of hydroxychloroquine to reflect possible, but very rare, irreversible eye damage reduced predicted uptake of the drug, lead to oral methrotrexate having the highest predicted uptake (92%) and reduced the predicted uptake of hydroxychloroquine to 82%.

Varying the attribute levels of the proposed treatments, the lowest uptake of the leading preventative treatment was 84% in first-degree relatives, 88% in RA patients, and 84% of all respondents. For first-degree relatives, the lowest uptake of the leading preventative treatment (84%) occurred in the scenarios where the health care providers were indifferent methotrexate, indifferent to any treatment, or when methotrexate had major irreversible side effects. Whereas for RA patients, the lowest uptake (88%) for the leading preventative treatment occurred when health care providers were indifferent to any treatment.

In first-degree relatives, oral methotrexate generally had the highest probability of uptake ranging from between 84% to 94%. Only when hydroxychloroquine had the same risk reduction of RA as methotrexate, hydroxychloroquine had a higher probability of uptake (93%) compared to oral methotrexate (91%). Uptake of biologic treatments in first-degree relatives compared to any other treatment were lower in every scenario, the uptake of biologics ranged from 45% to 53% for infusion rituximab , 60% to 67% for injectable abatacept and 61% to 69% for infusion abatacept. Uptake of biologic treatments was the highest in first-degree relatives when the health care providers was indifferent to any of the treatments.

Uptake of treatments varied when adjusting treatment attribute levels in RA patients. Depending on the scenario, injectable methotrexate, hydroxychloroquine and injectable steroids were the treatments that had the highest probability of uptake. RA patients had greater uptake of biologic treatments compared to first-degree relatives, the uptake of biologics ranged from 73% to 89% for infusion rituximab, 85% to 94% for injectable abatacept and 83% to 93% for infusion abatacept. A summary preventative treatment uptake in different scenarios can be found in Table **3-18** and **Appendix A.4 to A.18**.

Table 3-18: Summary of Sensitivity Analysis on Preventative Treatment Uptake Compared to No Treatment in First-Degree Relatives, Patients, and Overall

	Uptake of Top 5 Treatments Compared to No Treatment Options		
Treatment Change	**First-Degree Relatives**	**Patients**	**Overall**
None	91% Oral MTX 83% HCQ 81% Oral Steroid 73% Injectable MTX 72% Statin	96% Injectable MTX 95% Oral MTX 92% HCQ 87% Injectable Steroid 85% Injectable ABA	92% Oral MTX 86% HCQ 82% Oral Steroid 80% Injectable MTX 73% Statin
Risk Reduction of RA from 44 to 34 in HCQ	93% HCQ 91% Oral MTX 80% Oral Steroid 73% Injectable MTX 71% Statin	97% HCQ 96% Injectable MTX 95% Oral MTX 87% Injectable Steroid 85% Injectable ABA	94% HCQ 92 % Oral MTX 82% Oral Steroid 80% Injectable MTX 73% Statin
Health Care Provider Indifferent For MTX	84% Oral MTX 83% HCQ 80% Oral Steroids 71% Statin 60% Infusion ABA	92% HCQ 87% Injectable MTX 86% Oral MTX 85% Infusion ABA 85% Oral Steroid	86% HCQ 85% Oral MTX 82% Oral Steroid 73% Statin 65% Injectable MTX
MTX Side Effects Adjusted to Minor Reversible and Major Irreversible	84% Oral MTX 83% HCQ 80% Oral Steroid 71% Statin 61% Infusion ABA	93% Injectable MTX 92% Oral MTX 92% HCQ 87% Injectable Steroid 85% Injectable ABA	84% Oral MTX 83% HCQ 80% Oral Steroid 71% Statin 61% Infusion ABA

Respondent treatment preferences varied depending on the how the treatment levels were adjusted. Hydroxychloroquine was the preferred treatment when either its risk reduction of RA changed from 44 to 34 for hydroxychloroquine or when the health care provider was indifferent to methotrexate. Methotrexate was the preferred treatment when either its side effects were adjusted to minor reversible and major irreversible or when hydroxychloroquine side effect was adjusted to minor and major reversible. Oral Steroids were preferred when the healthcare provider was indifferent to any treatment. Depending on the scenario between 2.2% to 3.6% of respondents choose no treatment. No treatment was the highest (3.6%) when healthcare providers were indifferent to any treatment and to methotrexate. No treatment was at its lowest (2.2%) when the risk reduction of hydroxychloroquine changed from 44 to 34.

First-degree relative's treatment preferences were similar to the overall respondent preferences. The majority preferred a treatment that was administered orally and had a high risk reduction of RA. Methotrexate was the treatment that was the highest in these two attribute levels. Even when the side effects of methotrexate were changed to minor revisable and serious irreversible, oral methotrexate was preferred by 22% of first degree relatives followed by hydroxychloroquine (21%). Preferences for biologics were generally low with except if the health care provider was indifferent to any treatment. In this scenario, the uptake of infusion of abatacept was 9%, injectable abatacept was 8%, and infusion rituximab was 5%. No treatment was at its lowest (2.6%) when the risk reduction of RA for hydroxychloroquine was increased from 44 to 34 2.6 and at its highest (4%) when health care providers were indifferent to treatment.

RA patients had the preferences for preventative treatment changed depending on the scenario. Hydroxychloroquine was most preferred when health care providers were indifferent to methotrexate (21%) or the risk reduction of hydroxychloroquine was reduced from 44 to 34 (19%). Injectable methotrexate was the most preferred in all other scenarios even when its side effects were adjusted to minor reversible and major irreversible (19%). RA patients had higher preferences for biologics than first-degree relatives, preferences ranged from 2.8 to 5.2 % for infusion rituximab, 5.1 % to 11.2% for injectable abatacept and 5.4% to 9.4% for infusion abatacept. Only 1% to 2% of RA patient preferred no treatment.

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A summary of preventative treatment preferences is provided for all respondents, first degree relatives and RA patients in **Table 3-19** and **Appendix A.4 to A.18.**

Table 3-19: Summary of Sensitivity Analysis on Preventative Treatment Uptake Compared to All Treatment Options in First-Degree Relatives, Patients, and Overall

	Uptake of Top 5 Treatments Compared to All Treatment		
Treatment Change	**First-Degree Relatives**	**Patients**	**Overall**
None	35% Oral MTX 14% Oral Steroid 13% HCQ 9% Injectable MTX 9% Statin	27% Injectable MTX 14% Oral MTX 13% HCQ 9% Injectable Steroid 7% Injectable ABA	32% Oral MTX 16% HCQ 12% Oral Steroid 11% Injectable MTX 8% Statins
Risk Reduction of RA from 44 to 34 in HCQ	34% HCQ 26% Oral MTX 11% Oral Steroid 7% Injectable MTX 6% Statin	19% HCQ 15% Injectable MTX 14% Oral MTX 13% Injectable Steroid 11% Injectable ABA	33% HCQ 26% Oral MTX 10% Oral Steroid 9% Injectable MTX 6% Statin
Health Care Provider Indifferent For MTX	20% Oral MTX 20% HCQ 16% Oral Steroid 11% Injectable MTX 10% Statin	21% HCQ 13% Injectable MTX 12% Oral MTX 12% Injectable Steroid 11% Injectable ABA	21% HCQ 20% Oral MTX 16% Oral Steroid 11% Statin 7% Infused ABA
MTX Side Effects Adjusted to Minor Reversible and Major Irreversible	22% Oral MTX 21% HCQ 17% Oral Steroid 10% Statin 7% Infusion ABA	19% Injectable MTX 17% HCQ 17% Oral MTX 10% Injectable Steroid 9% Infusion ABA	21% Oral MTX 20% HCQ 15% Oral Steroid 10% Statin 7% Injectable MTX

3.4 **Discussion**

This thesis chapter focuses on eliciting and understanding the preferences of patients and FDRs who are a group at high risk of RA around potential preventative treatments for RA, and estimating the potential uptake of these treatments. Current clinical trials that are evaluating potential preventative treatments for RA are powered on the potential benefits, and there is an implicit assumption that people would be willing to take these treatments to reduce their risk of RA. My results challenge this assumption and highlight attributes that are strongly valued by RA patients and their first-degree relatives that can be expected to influence uptake of treatment. The DCE results suggest that people preferred treatments that offer a high risk reduction of RA, are administered orally, and are also preferred by the person's health care provider. Predicting the uptake of potential preventative treatments using these results indicated that oral methotrexate might be a treatment that maximizes the preferences of 70% of my sample, 72% of first-degree relatives. Methotrexate also had the highest probability of uptake (92%) compared to no treatment. Hydroxychloroquine was the second most preferred treatment maximizing the preferences of 20% of our sample, 19% of first-degree relatives and had an 85% probability of uptake. When considering preventative treatment, method of administration was an important factor for first-degree relatives. In first-degree relatives, treatments that were given through either injection or infusion had generally lower probabilities (45-73%) of uptake compared to oral treatments (72-91%). The biologic treatments currently under study were not expected to be the preferred treatment of many individuals and predicted uptake was low.

The performance of methotrexate was somewhat surprising, given that there is a perception that this drug can be quite toxic, leading to nausea, asthmatic symptoms, mouth ulcers, fatigue and

general feelings of unwellness. However, the drug is considered by others as generally a safe medication that is well tolerated at low dosages used to treat arthritis (104). The predicted preferred treatment was sensitive to assumptions about the expected level of risk reduction of methotrexate relative to hydroxychloroquine, which was predicted as the next best treatment for preference of my respondents and in terms of likely uptake. Adjusting the attribute levels describing current preventative treatments under study in sensitivity analyses found that changing the preference of the health care provider had the greatest impact on predicted treatment uptake. Changing the health care provider from preferring methotrexate (oral, or injectable) to being indifferent about this option reduced the uptake of preventative treatment to 84% in first-degree relatives, 92% in RA patients, and 86% in all respondents. After this change, Methotrexate was still predicted to be the preferred treatment for first-degree relatives (20%) however in RA patients their predicted preference for treatment changed to hydroxychloroquine (21%). Changing the predicted effectiveness of hydroxychloroquine in preventing RA, increased uptake of preventative treatment to 93% in first-degree relatives, 97% in RA patients, and 94% in all respondents. With this change, Hydroxychloroquine was the predicted preferred treatment for first-degree relatives (34%) and RA patients (19%).

Despite ongoing clinical trials (26,27,70) for preventative treatments in those at high risk of RA, to date there has been limited research into preferences around and uptake of preventative treatment options in this population (82). Previous studies have centered around preferences for RA treatment primarily in RA patients (84,85). One study in long-term RA patients suggested that this population prefers treatments that are low cost, have minimal adverse effects, lower in frequency of administration, and efficacious (84). These preferences are different when

compared to early RA patients who preferred treatments that were high in benefits, low in risks of permanent and serious side effects, and not administered through infusion (85). These differences in preferences between long-term and early RA suggest that preferences around RA treatments may change over time especially around dosing frequency and administration. If treatment preferences change over time in RA, it is likely that treatment preferences in individuals who are at high risk of RA are different from early and long-term RA patients. This could explain the apparent higher predicted uptake of treatments in the DCE that were given either as an infusion or injection in RA patients compared to first-degree relatives. Lower uptake and preference were predicted for treatments given either as an infusion or injection in first-degree relatives could be because they are generally injection naïve a factor that may influence preferences around treatment (81). Another reason could be that the health care provider did not prefer the majority of treatments given by infusion or injection, potentially because health care providers are likely to be more cautious in asymptomatic individuals, biologics have the potential for more serious side effects, and because of the huge costs of biologics.

The expected uptake of biologics drugs currently under study compared to hydroxychloroquine highlights that even if biologics are found to deliver a fairly substantial risk reduction, it is expected that those at high risk of RA would be reluctant to take them. This finding suggests there is a role for more careful consideration of preferences of potential recipients of treatment before embarking on expensive clinical trials. Interestingly, there are no current studies for oral or injectable methotrexate as preventative treatment, treatments the DCE results suggest may be a better candidates in terms of acceptability to my respondents and the predicted uptake than some of the other treatments (e.g. biologics) that are under study.

The only other study of preferences for prevention reported that the predicted uptake of a preventative therapy for RA in an at-risk population would be around 33% (82).This figure was based on the number of individuals who said 'yes' to a hypothetical treatment that was described to them in a binary choice scenario. In my DCE, across all respondents 67% of people indicated that they would take their preferred treatment compared with nothing for now. This varied by group with RA patients accepting their preferred treatment 76% of the time, while first degree relatives accepting their preferred treatment 66% of the time. My results are likely higher than Finch et al. (2016) because my DCE asked respondents to choose between two treatments then asked whether they wanted to keep their chosen treatment which may have led to more individuals choosing treatment instead of nothing for now.

In this study, my analysis which attempted to characterize the treatments that are currently under trial at the moment, suggested that compared with no treatment, uptake might be around 45% to 83%. Similar to previous results, I found that increasing effectiveness of treatment is a key driver of uptake, however Finch et al. (2016) found that serious adverse events were not as dominant as in my results. Mode of administration was not important in their study, Finch et al. (2016) suggest that this because individuals are making trade-offs between risks and benefits of treatment, in comparison the relative importance of mode of administration isn't as high. However potentially their finding could be driven by that they used relative risk reduction of RA rather than absolute risk reduction of RA which could have led to denominator neglect in respondents (88). My findings suggest that mode of administration is of equal or greater importance to the risks and benefits treatment. Another study evaluating the use of preventative

medication patients evaluating preventative medication for osteoporosis found that the route of treatment administration was considered by patients to be just as important as adverse events (105). This study also found similar to Finch et al. (2016) patients were more likely to take preventative treatment when the risk of developing osteoporosis increased (105). In the qualitative analysis, I identified two additional attributes uncertainty in estimates and health care provider preference that were important in preventative treatment decision making which were not included in Finch et al. (2016) study. Both of these attribute significantly affected preferences, especially health care provider preference, and consequently treatments that the health care provider did not prefer had low predicted uptake. These results could have also been higher because of the positive framing of attributes which may frame treatment more favorably, simplified attribute level descriptions for risks which may underplay the seriousness of side effects, high baseline risk which might promote a greater willingness to accept risks of treatment, and high positive predictive value of the test. All of these biases could have inclined respondents to choose treatment over no treatment.

Health care provider preference was a factor that was suggested to be important to first-degree relatives in the **Chapter 2** qualitative Framework analysis. Health care provider preference is important to first degree relatives because health care providers are often more knowledgeable about treatment options than their patients. With healthcare providers acting on behalf of the patient to maximize their utility, these finding underline the need for good patient-physician communication to understand patient preferences so that doctors can provide treatments that are in line with them.

Differences in treatment preferences and uptake could exist between those at high risk of RA and RA patients is because those at high risk of RA are generally asymptomatic. Asymptomatic people may have greater aversion to treatment in general, lower risk tolerance for side effects, and different treatment preferences compared to the population diagnosed with RA, because there is no experience of symptoms which would trigger treatment seeking behavior. Findings from this DCE suggest that in order for preventative treatments to be considered by those at high risk of RA they would have to be orally administered, preferred by the health care provider and have a high risk reduction of RA. Previous work by Finckh et al. (2016) in those at high risk of RA also found that treatments needed to have a high risk reduction of RA in order to be considered by those at high risk of RA. However, in the study by Finckh et al., mode of administration was not associated with the decision to take preventative treatment which may suggest that this group placed a higher value on other attributes than method of administration. Few studies (106,107) have looked at perspectives around preventative treatment in high risk individuals, and none have included the perspectives of those who could be recommending or providing these preventative treatments as potential determinants of preferences. The preference of the health care provider was identified as an attribute that would be important in the consideration of preventative treatment especially to treatment naïve individuals in my qualitative study, and has not been included in previous DCEs around RA treatments. For this reason I think my DCE has added to the literature.

A significant strength of this study was that the key attributes in the DCE around preventative treatment decision making were elicited from RA patients, first-degree relatives of patients, and rheumatologists in a formally analyzed qualitative study. Qualitative methods are now widely

recommended for developing DCEs and in the formal analysis and development of DCEs, the nuances of discussions in these three groups are incorporated and used to add greater understanding to the area around preventative treatments for RA. This qualitative work is currently being drafted for publication as a standalone contextual piece, a contribution to a limited area of literature.

However, there are also limitations of this work that merit discussion. There are limitations of DCEs including that the study design and the questions asked might affect individual responses due to framing effect (89). For example, a different description of the risk of side effects, background risk of RA and attribute levels might have resulted in different responses. Our background risk of RA was framed as 60 in 100 which may have made more respondents to consider taking preventative treatment due to this positive framing of the risk. In the DCE, one attribute describes both the risk and seriousness of treatment side effects. To fully describe the risk and seriousness of treatment side effects, more than one attribute may have been needed to describe the risks, seriousness, and types of side effects. If this the side effects were described in more detail, it is likely that the predicted uptake of treatments would be lower and the relative value place on this attribute would be higher. Adding more levels to describe side effects, increases the number of coefficients that I would have needed to estimate which requires a larger sample size. This would also lead to a more complex design and choice task for respondents to what I thought was already a fairly difficult DCE.

I also don't know if responses reflected true preferences since the scenarios presented were hypothetical. Studies have found that there is a definite difference between stated preferences

and actual preferences (108). My DCE scenarios could have difficult to complete, stressful thinking about the potential consequences of their choices, may have made some people uncomfortable as they are considering whether they are high risk despite that my ethics approval classified the DCE as low risk.

Important limitations of the DCE analysis were that first-degree relatives and RA patients were identified through survey responses. As well, in Amazon Mechanical Turk first-degree relatives were not referred to complete the survey by RA patients. It is not possible to verify the RA diagnosis of patients or whether first-degree relatives actually had a family member with a RA diagnosis. It is possible that first-degree relatives may have had a family member with another musculoskeletal symptom that is referred to as arthritis such as osteoarthritis, additional questions were asked to verify whether the family member did in fact have RA. Additionally, it is difficult to determine whether the first-degree relatives included in the DCE are in fact representative of individuals at high risk of RA. This is because the presence of other risk factors such as seropositive antibodies and smoking are not known in first-degree relative respondents. Finckh et al. (2016) were able perform a stated choice survey with confirmed first-degree relatives who were tested for genetic and immunologic biomarkers for RA. However, a limitation of their study was that their sample size was insufficient for some their statistical models and sub-group analyses. As well, since DCE responses were completed anonymously I was unable to contact respondents to verify whether if fact they did have RA or were a first-degree relatives of someone with RA. Secondly, RA patient DCE responses may be influenced by treatments that they are currently or have previously taken. This experience effect likely would lead RA patients to choose treatments similar to those they are currently taking rather than

would have been their preferred choice ex ante because their preferences are likely to change based on their experience with RA. Therefore, RA patient preferences may not reflect the preferences of those who are at high risk of RA who are mostly a treatment naïve population. Thirdly, first-degree relative responses may be influenced by treatments that their family member with RA has had experience with. This second-hand experience effect may likely lead to first-degree relatives to choose or avoid treatments with similar attributes to the treatments their relative is on. Lastly, our sample had a high proportion of male respondents (40%) which may affect the generalizability of our results because RA disease that has approximately a 3 to 1 female to male sex ratio (2). A higher proportion of male respondents in our sample could affect the generalizability of our predicted uptake of preventative treatment and different relative values of the attribute levels due to differences in health seeking behavior (109) and treatment preferences (110) in the male population.

Nevertheless, despite these limitations this DCE provides understanding of preferences around and the likely uptake of potential preventative treatments for RA. The DCE findings emphasize the importance of health care provider preferences and oral administration for the uptake of preventative treatment in those who are at high risk of RA compared to RA patients. This suggests that trials of existing non-biologic DMARDs are likely to be those policy makers should be paying most attention to for results as they are likely to have the greatest chance of being a preventative treatment option which is affordable and likely to have reasonable uptake depending on how effective they are reducing the risk of RA. Furthermore, since the preferences of those at high risk of RA, health care providers and policy makers vary, it would be worthwhile to develop a tool that allows them to enter the attribute levels that they think best represent treatment

options they are considering so that they can predict what their preferences for and likely uptake of treatment would be.

Chapter 4: Conclusion

Clinical trials (26,27) evaluating the effectiveness of preventative treatment in delaying or stopping progression of RA in high risk individuals will be reporting their results within the next 2 years. The overarching objective of this thesis is to understand preferences for preventative treatment programs in order to guide how these results can be best implemented at the population level.

Qualitative analysis of focus groups including patients, first-degree relatives, and rheumatologists in **Chapter 2** has allowed for the identification of important attributes which describe the key considerations around preventative treatment options. Presenting these attributes identified in **Chapter 2** in a DCE in **Chapter 3** elicits the value that patients and first-degree relatives of patients (high-risk individuals) place on the attributes and how they trade-off these attributes. Through the analysis of DCE responses from these groups, the important factors that would influence uptake of a preventative treatment have been identified and the willingness to trade-off between levels of one attribute for increased benefit in another attribute has been determined. Finally, the potential uptake of different treatments currently being studied as potential preventative strategies has been predicted. In this final chapter, results from the qualitative Framework analysis and DCE are summarized, strengths and limitations of this thesis are discussed, and recommendations for future research are provided.

4.1 Summary of Key Findings

To understand preferences for preventative treatment programs, it was important to first understand what aspects of preventative treatment are important from the perspectives of those

who might be expected to consider preventative treatment and also those of physicians/healthcare providers who might be expected to deliver a preventative treatment program. The qualitative Framework analysis of transcriptions of RA patients, RA patient's first-degree relatives and rheumatologist focus groups conducted in **Chapter 2**, elicited attributes to be included in a DCE. Risk and type of side effects, certainty in estimates and the opinion of the health care provider were three important factors in the decision-making process around the consideration of a preventative treatment program for RA. This qualitative work has filled a current gap in literature by providing insight from rheumatologists who may be expected to support decisions of the individuals at high risk of RA for whom a preventative treatment might be recommended, first-degree relatives who are a proxy for those at high risk of RA (since genetics are a key risk factor for RA), and patients who may be involved in the decisions of their at-risk relatives because of their experience with the disease and the types of treatments that may be offered.

Chapter 3 then presents the treatment attributes elicited in **Chapter 2** in a DCE study to obtain the preferences for and relative value of each of these attributes in decisions about preventative treatment. Using the preferences and relative value of each attribute, the DCE results have identified the features that will determine the likely acceptability of treatments and predict the probability of successful uptake and implementation in a preventative treatment program for RA. The features of treatments that most strongly determined preferences were those that are preferred by the health care provider, given orally, and offer a reasonably high risk reduction of RA, the risk of side effects and the certainty of evidence also significantly influenced preferences, but to a lesser degree. The analysis of DCE identified optimal current treatments,

some of which are under study that will maximize these requirements. These treatments were oral methotrexate, hydroxychloroquine and oral steroids. The two biologics (abatacept and rituximab) being currently studied are unlikely to meet the requirements of asymptomatic people asked to consider treatment. Two options methotrexate and oral steroids are potential options, however they are not currently under study and therefore not likely to be offered for preventative treatment any time soon. These findings highlight the importance of understanding the preferences of target populations to better prioritize research funding.

4.2 Strengths and Limitations of this Research

This thesis has used rigorous qualitative and quantitative methods to understand the necessary features required for the uptake and implementation of a preventative treatment program for RA, and identify current treatments that may be acceptable to those at high risk of RA. However, in the two studies undertaken in this thesis there are several strengths and limitations that merit discussion.

The qualitative focus groups performed in **Chapter 2** allowed for perspectives around RA and preventative treatments for RA to be discussed in great depth and detail. This allowed for valuable insight into what attributes around preventative treatments were important to each of these groups and how these attributes could be used in the design of a DCE. Undertaking the focus groups in two rounds allowed for verification of the attributes elicited in the first round of interviews before their inclusion in the DCE. Additionally, these focus groups were facilitated without the direct involvement of the researcher, which prevented subject bias in participant discussions. Lastly, interview transcripts were coded independently by two researchers

(Katherine Milbers and myself) in consultation with a qualitative expert (Dr. Sarah Munro) allowing for each transcript to be reviewed thoroughly and for all relevant themes to be identified in the transcript.

Limitations of this qualitative analysis included that all focus groups were conducted in English, limiting my ability to investigate whether there were cultural differences between French and English speakers on perspectives around RA and preventative treatment for RA. Furthermore, these focus groups were conducted in a Canadian population, which limit the applicability of findings to other jurisdictions that may have different models of health care delivery, demographics and culture. Qualitative research can be significantly influenced by both the skill and biases of the researcher, which may influence research findings. To mitigate this risk of personal biases and qualitative research skills influencing the findings, I received methodological guidance from a qualitative expert (Dr. Sarah Munro) and a second researcher (Katherine Milbers) reviewed the interview transcripts independently then consolidated our findings.

Strengths of the DCE performed in **Chapter 3** include the separation of patient and first-degree relative groups to determine preferences for and uptake of preventative treatment since preferences might be expected to differ between these groups. Another significant strength of this chapter was that the key attributes in the DCE around preventative treatment decision making were elicited from RA patients, first-degree relatives of patients, and rheumatologists in a formal qualitative study. This allowed to the development of a survey that could be administered to all these groups to see how concordant preferences were. Qualitative methods are now widely recommended for developing DCEs and in the formal analysis and development

of DCEs, the nuances of discussions in these three groups are incorporated and used to add greater understanding to the area around preventative treatments for RA.

Limitations include that DCE responses from rheumatologists were not obtained, RA diagnosis of patients or first-degree relatives of RA patients were not confirmed, there is uncertainty around the attribute levels that describe each of the preventative treatment options and potential biases that may influence our predicted uptake of preventative treatment. The qualitative work in **Chapter 2** suggested the importance of health care provider in the decision of whether to undertake preventative treatment, originally in the DCE the recruitment of rheumatologists was planned however recruitment challenges has currently limited their involvement. Another limitation with my respondents was that it is not possible to verify the RA diagnosis of patients or whether first-degree relatives actually had a family member with a RA diagnosis. It is possible that first-degree relatives may have had a family member with another musculoskeletal symptom that is referred to as arthritis such as osteoarthritis. To try to overcome this limitation, additional questions were asked to try to verify whether the family member did in fact have RA. Since DCE responses were completed anonymously I was unable to contact respondents to verify whether if fact they did have RA or were a first-degree relatives of someone with RA. Lastly, there is uncertainty around the levels that describe each of the potential preventative treatments. It is difficult to know the actual risk reduction of RA and health care provider's preference for each treatment and individual health care provider's preferences may potentially vary for a single treatment. Additionally, it is difficult to describe the specific side effects of each the treatments. This limitation may have led to hyperbolic discounting of side effects. This may influence individual preferences for each of the treatments by making them more likely to choose

treatments that have more severe types of side effects. Lastly, the positive framing of attributes and positive predictive value of the test that would predict whether the individual would develop RA could lead to individual preferences towards treatment compared to no treatment. Nevertheless, despite these limitations this DCE provides understanding of preferences around and the likely uptake of potential preventative treatments for RA.

4.3 Future Research and Recommendations

Overall, this thesis has determined the important attributes for the uptake of preventative treatment for RA in patients and first-degree relatives. However, there is still further research that to be done in this area. Further research should explore preference heterogeneity in preferences in this sample as treatment preferences may vary based on respondent baseline RA risk, length of RA in their first-degree relatives, and risk tolerance. Preference heterogeneity could also be explored through latent class analysis to identify whether there are any identifiable sub-groups with similar preferences. As suggested previously, if the results are accurate they suggest that there are two potential preventative treatments that would have a high expected uptake in high-risk individuals that are not currently under study. In contrast, there are two treatments that the results of this thesis suggest would have low uptake in high-risk individuals that are being studied.

These findings highlight the importance of understanding preferences around healthcare interventions before clinical trials are started and treatments are provided. With limited amounts of research and health care funding, it is important to make informed decisions around what projects are funded and treatments are provided so that these limited amounts of funding are used

to their maximal effectiveness. Providing treatments and services that have low uptake and funding research around them is an inefficient use of these limited amounts of funding. To determine what should be funded, it is important to identify the potential treatments, products or services would be acceptable to their intended users and are predicted to have a high probability of uptake which can be done through a DCE. From the results of a DCE, key funding areas can be identified and projects that expand upon treatments, services and interventions that have a high predicted uptake and preference for can be prioritized.

Another area of further research is within First Nations populations, where RA occurs at least twice the rate of the general population (14), at an earlier age (15), and with increased severity (15). A study (111) focused on developing programs for the prevention of diabetes, a condition that has a 3-5 times higher prevalence in First Nations compared to the Canada population (112,113), found that active involvement of community members is an important factor in the success of the program and programs needed to be tailored to each First Nation community. This study highlights the value in undertaking qualitative research and potentially a DCE in the First Nations population, as their preferences for preventative treatment are likely to be different compared to the general public.

4.4 **Conclusion**

This thesis has elicited preferences of those who are at high risk of RA around preventative treatment and provided suggestions on how these preferences can be best implemented in preventative treatment programs. A qualitative Framework analysis of focus groups obtained the key attributes that are involved in decisions around whether or not to take preventative treatment

and thus could be included in the DCE. This was derived from the key participants in decisions about whether or not to take preventative treatments for RA, which included first-degree relatives, patients, and rheumatologists. Patients and first-degree relatives focused significantly on maintaining their current quality of life, which centered on avoiding side effects of medications, maintaining their employment, and continuing to live an active lifestyle. Rheumatologists focused largely on the evidence for preventative treatment and the risk and types side effects of preventative treatment. From this qualitative analysis, seven different potential attributes and attribute levels were elicited to be included in a DCE. In the DCE, five of these attributes which related to treatment were included to determine patients' and first-degree relatives preferences for these attributes, which described the potential preventative treatment options, the trade-offs they make between these attributes, and predict the acceptability and uptake of potential these preventative options. The DCE findings show that those at high-risk of RA place a high value on health care provider preferences and oral administration when evaluating preventative treatment options as compared to RA patients. These findings highlight the need for research exploring preventative treatment programs to be conducted in the population that they are aimed towards, as their preferences may differ from the general RA population.

There are currently ongoing clinical trials for preventative treatments being undertaken both in Europe and the USA that aim to prevent and minimize the progression to RA in high-risk individuals. With these clinical trials reporting their results within the next 2 years, it will be necessary for decision makers to understand preferences of those who are at high risk of RA for preventative treatments and guide how these preferences can be best implemented in preventative treatment programs. This thesis has identified preferences that drive decision making in the context

of a preventative treatment and potential preventative treatments that would be acceptable to those who are at high-risk of RA.

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Appendices

Appendix A

A.1 Forced Choice Effects Coded Conditional Logit Model

	Coefficient	z	P
Risk Reduction of RA			
From 66 to 44	-0.43		
From 66 to 34	.03	.99	.32
From 66 to 24	.41	14.86	<0.001
Route of administration			
Infusion	-.40		
Injection	-.17	-6.57	<0.001
Oral	.57	20.90	<0.001
Side Effect			
Minor Reversible, Serious Irreversible	-.56		
Minor reversible, Serious reversible	.26	10.04	<0.001
Minor reversible	.30	11.13	<0.001
Certainty in Estimates			
Very little	-.21		
Limited	-.07	-2.69	.007
Moderate	.27	10.76	<0.001
Preference of Health Care Provider			
Health care provider does not prefer	-.45		
Indifferent	.04	1.46	.145
Health care provider prefers	.41	15.1	<0.001
No. of responses	10746		
No. of respondents	597		
Log-likelihood	-2928.67		

A.2 Coefficients of Effects Coded Logit Model with Random Effects for Opt-Out

	Coefficient	z	P
Risk Reduction of RA			
From 66 to 44	-0.802		
From 66 to 34	0.148	2.39	0.017
From 66 to 24	0.653	10.49	<0.001
Route of administration			
Infusion	-0.341		
Injection	-0.362	-5.54	<0.001
Oral	0.703	11.13	<0.001
Side Effect			
Minor Reversible, Serious Irreversible	-0.523		
Minor reversible, Serious reversible	0.131	2.13	0.033
Minor reversible	0.393	6.19	<0.001
Certainty in Estimates			
Very little	-0.347		
Limited	-0.106	-1.68	0.093
Moderate	0.453	7.18	<0.001
Preference of Health Care Provider			
Health care provider does not prefer	-0.406		
Health care provider is indifferent	-0.176	-2.90	0.005
Health care provider prefers	0.582	9.45	<0.001
Constant	1.002	7.93	<0.001
No. of observations	5346		
No. of respondents	594		
Log-likelihood	-2405.67		

A.3 Coefficients of Effects Coded Logit Model with Random Effects for RA Patients for Opt-Out

	Coefficient	z	P
Risk Reduction of RA			
From 66 to 44	-0.682		
From 66 to 34	0.236	1.58	0.114
From 66 to 24	0.446	2.99	0.003
Route of administration			
Infusion	-0.081		
Injection	0.100	0.64	.522
Oral	-0.019	-0.13	.894
Side Effect			
Minor Reversible, Serious irreversible	-0.509		
Minor reversible, Serious reversible	0.092	0.64	0.522
Minor reversible	0.416	2.74	0.006
Certainty in Estimates			
Very little	-0.382		
Limited	0.133	0.92	0.360
Moderate	0.249	1.66	0.098
Preference of Health Care Provider			
Health care provider does not prefer	-0.320		
Health care provider is indifferent	-0.428	-3.00	0.003
Health care provider prefers	0.748	4.99	<0.001
Constant	1.824	6.80	<0.001
No. of responses	981		
No. of respondents	109		
Log-likelihood	-414.563		

A.4 Coefficients of Effects Coded Logit Model with Random Effects for First-Degree Relatives for Opt-Out

	Coefficient	z	P
Risk Reduction of RA			
From 66 to 44	-0.853		
From 66 to 34	0.134	1.95	0.051
From 66 to 24	0.721	10.28	<0.001
Route of administration			
Infusion	-0.410		
Injection	-0.467	-6.30	<0.001
Oral	0.877	12.27	<0.001
Side Effect			
Minor Reversible, Serious irreversible	-0.528		
Minor reversible, Serious reversible	0.133	1.94	0.052
Minor reversible	0.395	5.60	<0.001
Certainty in Estimates			
Very little	-0.330		
Limited	-0.177	-2.66	0.008
Moderate	0.507	7.30	<0.001
Preference of Health Care Provider			
Health care provider does not prefer	-0.449		
Health care provider is indifferent	-0.123	-1.72	0.085
Health care provider prefers	0.572	8.31	<0.001
Constant	0.790	5.57	<0.001
No. of responses	4365		
No. of respondents	485		
Log-likelihood	-1962.411		

A.5 Predicted Uptake for Preventative Treatment

Treatment	Uptake Compared to No Treatment	Uptake Compared to All Treatment Options
No Treatment	**X**	2.8%
Oral MTX	92.1%	32.2%
Injectable MTX	80.1%	11.1%
Hydroxychloroquine	93.8%	16.2%
Infused ABA	66.6%	5.5%
Injectable ABA	66.2%	5.4%
Infused RTX	50.9%	2.9%
Injectable Steroid	60.5%	4.2%
Oral steroid	81.6%	12.2%
Statin	73.4%	7.6%

A.6 Predicted of Uptake of Preventative Treatments Compared to No Treatment

Uptake Compared to No Treatment		
Treatment	**First-Degree Relative (n=488)**	**Patient (n=109)**
Oral MTX	91.1%	95.3%
Injectable MTX	72.8%	95.8%
Hydroxychloroquine	83.3%	91.8%
Infusion ABA	61.2%	82.9%
Injectable ABA	59.8%	85.3%
Infusion RTX	44.9%	72.7%
Injectable Steroid	51.8%	86.7%
Oral Steroid	80.4%	85.3%
Statin	71.3%	77.6%

A.7 Predicted Uptake for Preventative Treatments Compared to All Treatment Options

Uptake Compared to All Treatment Options		
Treatment	**First-Degree Relative (n=488)**	**Patient (n=109)**
No Treatment	3.3%	1.2%
Oral MTX	33.6%	24.1%
Injectable MTX	8.8%	27.1%
Hydroxychloroquine	16.3%	13.3%
Infusion ABA	5.2%	5.7%
Injectable ABA	4.9%	6.9%
Infusion RTX	2.7%	3.1%
Injectable Steroid	3.5%	7.7%
Oral Steroid	13.5%	6.8%
Statin	8.2%	4.1%

A.8 Predicted Uptake for Preventative Treatment Adjusting Risk Reduction of RA from 44 to 34 in 100 for Hydroxychloroquine

Treatment	**Uptake Compared to No Treatment**	**Uptake Compared to All Treatment Options**
No Treatment	**X**	2.2%
Oral MTX	92.1%	25.6%
Injectable MTX	80.1%	8.8%
Hydroxychloroquine	93.8%	33.3%
Infused ABA	66.6%	4.4%
Injectable ABA	66.2%	4.3%
Infused RTX	50.9%	2.3%
Injectable Steroid	60.5%	3.4%
Oral steroid	81.6%	9.7%
Statin	73.4%	6.0%

A.9 Predicted of Uptake of Preventative Treatments in First-Degree Relatives and Patients Compared to No Treatment Adjusting Risk Reduction of RA from 44 to 34 in 100 for Hydroxychloroquine

Uptake Compared to No Treatment		
Treatment	**First-Degree Relative (n=488)**	**Patient (n=109)**
Oral MTX	91.1%	95.3%
Injectable MTX	72.8%	95.8%
Hydroxychloroquine	93.0%	96.6%
Infusion ABA	61.2%	93.4%
Injectable ABA	59.8%	94.4%
Infusion RTX	44.9%	88.6%
Injectable Steroid	51.8%	95.0%
Oral Steroid	80.4%	94.4%
Statin	71.3%	77.6%

A.10 Predicted Uptake for Preventative Treatments in First-Degree Relatives and Patients Compared to All Treatment Options Adjusting Risk Reduction of RA from 44 to 34 in 100 for Hydroxychloroquine

Uptake Compared to All Treatment Options		
Treatment	**First-Degree Relative (n=488)**	**Patient (n=109)**
No Treatment	2.6%	0.7%
Oral MTX	26.4%	13.5%
Injectable MTX	6.9%	15.2%
Hydroxychloroquine	34.3%	18.7%
Infusion ABA	4.1%	9.4%
Injectable ABA	3.8%	11.2%
Infusion RTX	2.1%	5.2%
Injectable Steroid	2.8%	12.6%
Oral Steroid	10.6%	11.2%
Statin	6.4%	2.3%

A.11 Predicted Uptake for Preventative Treatments Compared to All Treatment Options for First-Degree Relatives and Patients if Health Care Provider is Indifferent to Methotrexate

Treatment	Uptake Compared to No Treatment	Uptake Compared to All Treatment Options
No Treatment	**X**	3.6%
Oral MTX	84.6%	19.6%
Injectable MTX	65.4%	6.8%
Hydroxychloroquine	85.5%	21.0%
Infused ABA	66.6%	7.1%
Injectable ABA	66.2%	7.0%
Infused RTX	50.9%	3.7%
Injectable Steroid	60.5%	5.5%
Oral steroid	81.6%	15.9%
Statin	73.4%	9.9%

A.12 Predicted Uptake of Treatments in First-Degree Relatives and Patients Compared to No Treatment if Health Care Provider is Indifferent to Methotrexate

Uptake Compared to No Treatment		
Treatment	**First-Degree Relative (n=488)**	**Patient (n=109)**
Oral MTX	83.6%	86.3%
Injectable MTX	72.8%	87.6%
Hydroxychloroquine	83.3%	91.8%
Infusion ABA	61.2%	82.9%
Injectable ABA	59.8%	85.3%
Infusion RTX	44.9%	72.7%
Injectable Steroid	51.8%	86.7%
Oral Steroid	80.4%	85.3%
Statin	71.3%	77.6%

A.13 Predicted Uptake of Treatments in First-Degree Relatives and Patients Compared to All Treatment Options if Health Care Provider is Indifferent to Methotrexate

Uptake Compared to All Treatment Options		
Treatment	**First-Degree Relative (n=488)**	**Patient (n=109)**
No Treatment	4.0%	1.8%
Oral MTX	20.2%	11.5%
Injectable MTX	10.6%	12.9%
Hydroxychloroquine	19.7%	20.6%
Infusion ABA	6.2%	8.9%
Injectable ABA	5.9%	10.6%
Infusion RTX	3.2%	4.9%
Injectable Steroid	4.2%	11.9%
Oral Steroid	16.3%	10.6%
Statin	9.8%	6.3%

A.14 Predicted Uptake for Preventative Treatments Compared to All Treatment Options if Hydroxychloroquine Side Effects are Adjusted to Minor and Major Reversible

Treatment	Uptake Compared to No Treatment	Uptake Compared to All Treatment Options
No Treatment	**X**	2.9%
Oral MTX	92.1%	33.4%
Injectable MTX	80.1%	11.5%
Hydroxychloroquine	81.9%	12.9%
Infused ABA	66.6%	5.7%
Injectable ABA	66.2%	5.6%
Infused RTX	50.9%	3.0%
Injectable Steroid	60.5%	4.4%
Oral steroid	81.6%	12.7%
Statin	73.4%	7.9%

A.15 Predicted Uptake for Preventative Treatments in First-Degree Relatives and Patients Compared to All Treatment Options if Hydroxychloroquine Side Effects Are Adjusted to Minor and Major Reversible

Uptake Compared to No Treatment		
Treatment	**First-Degree Relative (n=488)**	**Patient (n=109)**
Oral MTX	91.1%	95.3%
Injectable MTX	72.8%	95.8%
Hydroxychloroquine	79.3%	89.1%
Infusion ABA	61.2%	82.9%
Injectable ABA	59.8%	91.1%
Infusion RTX	44.9%	72.7%
Injectable Steroid	51.8%	86.7%
Oral Steroid	80.4%	85.3%
Statin	71.3%	77.6%

A.16 Predicted Uptake for Preventative Treatments in First-Degree Relatives and Patients Compared to All Treatment Options if Hydroxychloroquine Side Effects Are Adjusted to Minor and Major Reversible

Uptake Compared to All Treatment Options		
Treatment	**First-Degree Relative (n=488)**	**Patient (n=109)**
No Treatment	3.4%	1.2%
Oral MTX	35.0%	23.7%
Injectable MTX	9.1%	26.7%
Hydroxychloroquine	13.1%	9.5%
Infusion ABA	5.4%	5.6%
Injectable ABA	5.1%	11.9%
Infusion RTX	2.8%	3.1%
Injectable Steroid	3.7%	7.6%
Oral Steroid	14.0%	6.7%
Statin	8.5%	4.0%

A.17 Predicted Uptake for Preventative Treatments Compared to All Treatment Options if Methotrexate Side Effects are Adjusted to Minor Reversible to Minor and Major Irreversible

Treatment	Uptake Compared to No Treatment	Uptake Compared to All Treatment Options
No Treatment	**X**	3.5%
Oral MTX	85.9%	21.1%
Injectable MTX	67.7%	7.3%
Hydroxychloroquine	85.5%	20.4%
Infused ABA	66.6%	6.9%
Injectable ABA	66.2%	6.8%
Infused RTX	50.9%	3.6%
Injectable Steroid	60.5%	5.3%
Oral steroid	81.6%	15.4%
Statin	73.4%	9.6%

A.18 Predicted Uptake for Preventative Treatments in First-Degree Relatives and Patients Compared to All Treatment Options Adjusting Methotrexate Side Effects are Adjusted to Minor Reversible to Minor and Major Irreversible

Uptake Compared to No Treatment		
Treatment	**First-Degree Relative (n=488)**	**Patient (n=109)**
Oral MTX	84.1%	91.8%
Injectable MTX	58.0%	92.6%
Hydroxychloroquine	83.3%	91.8%
Infusion ABA	61.2%	82.9%
Injectable ABA	59.8%	85.3%
Infusion RTX	44.9%	72.7%
Injectable Steroid	51.8%	86.7%
Oral Steroid	80.4%	85.3%
Statin	71.3%	77.6%

A.19 Predicted Uptake for Preventative Treatments in First-Degree Relatives and Patients Compared to All Treatment Options Adjusting Methotrexate Side Effects Adjusted to Minor Reversible to Minor and Major Irreversible

Uptake Compared to All Treatment Options		
Treatment	**First-Degree Relative (n=488)**	**Patient (n=109)**
No Treatment	4.1%	1.5%
Oral MTX	21.9%	17.2%
Injectable MTX	5.7%	19.3%
Hydroxychloroquine	20.6%	17.3%
Infusion ABA	6.5%	7.5%
Injectable ABA	6.2%	8.9%
Infusion RTX	3.4%	4.1%
Injectable Steroid	4.4%	10.0%
Oral Steroid	17.0%	8.9%
Statin	10.3%	5.3%

A.20 Predicted Uptake of Preventative Treatment Adjusting Health Care Provider Indifferent To Any Treatment

Treatment	Uptake Compared to No Treatment	Uptake Compared to All Treatment Options
No Treatment	**X**	3.6%
Oral MTX	84.6%	19.8%
Injectable MTX	65.4%	6.8%
Hydroxychloroquine	73.4%	10.0%
Infused ABA	71.5%	9.1%
Injectable ABA	71.1%	8.9%
Infused RTX	56.6%	4.7%
Injectable Steroid	65.9%	7.0%
Oral steroid	84.8%	20.2%
Statin	73.4%	10.0%

A.21 Predicted Uptake of Preventative Treatments in First-Degree Relatives and Patients Compared to No Treatment if Health Care Provider is Indifferent To Any Treatment

Uptake Compared to No Treatment		
Treatment	**First-Degree Relative (n=488)**	**Patient (n=109)**
Oral MTX	83.6%	86.3%
Injectable MTX	57.1%	87.6%
Hydroxychloroquine	71.3%	77.6%
Infusion ABA	68.6%	81.3%
Injectable ABA	67.4%	83.9%
Infusion RTX	53.0%	72.7%
Injectable Steroid	59.8%	85.4%
Oral Steroid	85.1%	83.9%
Statin	71.3%	77.6%

A.22 Predicted Uptake of Preventative Treatments Compared to All Treatment Options in First-Degree Relatives and Patients Adjusting Health Care Provider Indifferent To Any Treatment

Uptake Compared to All Treatment Options		
Treatment	**First-Degree Relative (n=488)**	**Patient (n=109)**
No Treatment	4.0%	2.2%
Oral MTX	20.5%	14.1%
Injectable MTX	5.3%	15.9%
Hydroxychloroquine	9.9%	7.8%
Infusion ABA	8.8%	9.8%
Injectable ABA	8.3%	11.7%
Infusion RTX	4.5%	6.0%
Injectable Steroid	6.0%	13.1%
Oral Steroid	22.8%	11.6%
Statin	9.9%	7.8%