Patient Understanding: The Impact Bias, Quality of Life Predictions, and Informed Consent

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TABLE OF CONTENTS

ABSTRACT

Contemporary research ethics is founded on the premise that patients must have an adequate understanding of the risks and benefits of participating in a clinical trial, including how these compare to choosing not to participate and receiving standard care, before agreeing to research participation. Patients should understand the probability that risks and benefits have of occurring and appreciate how these events may affect their well-being and quality of life (QoL) in order to ensure that they can make decisions that optimize their likely QoL, which may be important to their decision-making. Healthy individuals and patients are generally bad at predicting how their emotional state and QoL will be impacted by future events. Patients may therefore have a poor understanding of how their QoL will be impacted by the progression of their illness. In this thesis, I explore the implications of affective forecasting for consent validity in the context of clinical trials. In part 1, I outline how poor patient QoL predictions may impair their ability to provide a valid informed consent. In part 2, I describe research in the field of autoimmune disease, in which potentially risky therapies are being evaluated in trials where the ability of patients to provide informed consent may be particularly impaired. In part 3, I outline a research protocol that will help determine if patients with autoimmune disease have accurate expectations about their likely future QoL and if these expectations affect their enrolment decisions. Finally, in part 4, I describe the potential implications of this research on clinical trial recruitment, as research into affective forecasting in clinical trial enrolment may identify a novel method to improve patient understanding and the informed consent process and to promote patient autonomy.

RÉSUMÉ

L'éthique contemporaine de la recherche est fondée sur le principe que les patients doivent avoir une compréhension adéquate des risques et des avantages de la participation à un essai clinique, y compris la comparaison entre le choix de ne pas y participer et de recevoir des soins habituels, avant d'accepter de participer à la recherche. Les patients devraient comprendre la probabilité que les risques et les bénéfices se produisent et apprécier la manière dont ces événements peuvent affecter leur bien-être et leur qualité de vie afin de s'assurer qu'ils peuvent prendre des décisions qui optimisent leur qualité de vie, ce qui peut être important pour leurs décisions. Les individus en bonne santé et les patients ne sont pas généralement aptes à prédire comment leur état émotionnel et leur qualité de vie seront influencés par les événements futurs. Les patients peuvent donc avoir une mauvaise compréhension de la manière dont leur qualité de vie sera influencée par l'évolution de leur maladie. Dans cette thèse, j'explore les implications de la prévision affective pour la validité du consentement dans le contexte des essais cliniques. Dans la première partie, j'explique comment de mauvaises prévisions de la qualité de vie des patients peuvent nuire à leur capacité de donner un consentement éclairé valable. Dans la deuxième partie, je décris la recherche dans le domaine des maladies auto-immunes, dans laquelle des traitements potentiellement risqués sont évalués dans le cadre d'essais où la capacité des patients à donner leur consentement éclairé peut être particulièrement compromise. Dans la troisième partie, je présente un protocole de recherche qui permettra de déterminer si les patients atteints de maladies auto-immunes ont des attentes précises

quant à leur qualité de vie future et si ces attentes ont un impact sur leurs décisions d'inscription. Enfin, dans la quatrième partie, je décris les implications potentielles de cette recherche dans le contexte du recrutement des essais cliniques, car la recherche sur la prévision affective dans le recrutement des essais cliniques peut permettre d'identifier une nouvelle méthode pour améliorer la compréhension des patients et le processus de consentement éclairé et pour promouvoir l'autonomie des patients.

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Introduction

Patients with chronic illnesses make decisions concerning their medical treatment based on their current symptomatology, the risk of their illness progressing, the available treatments and those being researched, and many individual factors including their financial situation, risk tolerance and their goals and values. These decisions are therefore complex and theoretically require that the patient or their medical decision-maker understands each of these factors. Once each of these factors is explained to patients, they must consider all of their treatment options to come to an informed decision. This decision ideally gives them the highest probability, out of all of the available options, of achieving their unique current and anticipated goals and provides them with an optimal quality of life.

To make this informed decision, patients must understand not only their risk of progression and of new symptom development, as is often explained in the clinical setting by their treating healthcare team, but also how these symptoms will affect their quality of life. Patients must attempt to predict how the development of a variety of new symptoms will affect their future ability to function and perform activities they enjoy, as ultimately, it is these factors, among others, that patients are trying to optimize in choosing a treatment option. These decisions are greatly challenged when patients confront uncertainty about treatment options -- either because new treatment options have limited supporting evidence, or because new treatments are being evaluated within a clinical trial.

Recently, trials examining invasive and powerful treatments with potentially lethal side effects have been performed or proposed with the aim of halting disease progression in various chronic diseases. This is perhaps most notable in chronic autoimmune diseases, for which powerful immunomodulators and stem cell-based therapies have been examined. For example, studies have evaluated the ability of autologous hematopoietic stem cell transplantation and monoclonal antibody therapy to prevent the progression of multiple sclerosis and type 1 diabetes. Patients presented with the possibility of enrolling in such a clinical trial must consider the risks and potential benefits of participating, which are by definition uncertain, and factor this in when considering all treatment options. They must estimate what their future quality of life will be if they choose each available option (trial participation or non-participation and treatment with the available standard of care), and use these estimates to make a decision based on their individual risk tolerance and goals. These quality of life estimates are thus extremely important, as they are crucial to a patient's decision-making process and to their consenting to enrol in a clinical trial. Studies examining how subjects predict future emotional states, termed affective forecasting, have suggested that most people are poor predictors (overly optimistic or pessimistic) of how future events will impact their emotional well-being. Biases in predicting future emotional states will impact quality of life predictions, as emotional well-being is one of the many components of an individual's quality of life. Clinicians should therefore seek to help their patients accurately anticipate how their disease's progression will impact their emotions and quality of life and help them make better-informed decisions regarding their treatment. Researchers should consider how these forecasting biases might

impact the decision-making of patients considering enrolling in a clinical trial, as these forecasting biases may impact a patient's ability to provide informed consent. This issue is further complicated in certain fields of medicine, including paediatrics, where parents often make these complex decisions for patients and in areas of medicine where early markers have been identified that can accurately predict that a disease will develop prior to a patient experiencing symptoms. In this thesis, we review the affective forecasting literature, outline the implications of affective forecasting for consent validity, and describe a protocol that will identify how the quality of life predictions of recently diagnosed patients impact their epistemic forecasts and willingness to enrol in a hypothetical clinical trial.

Chapter 1:

Literature Review: Affective Forecasting Biases and their Ability to Impair Patient Understanding and their Ability to Provide a Valid Informed Consent

Autonomy, Informed Consent, and Understanding Quality of Life Changes

Respecting patient autonomy and ensuring patients provide an informed consent to be treated are fundamental principles of medical ethics [1]. Beauchamp and Childress define personal autonomy as “at a minimum, self-rule that is free from both controlling interference by others and from certain limitations such as an inadequate understanding that prevents meaningful choice” [1]. They argue that choices exist on a continuum of autonomy, with complete autonomy on one end and a completely non-autonomous decision on the other [1]. They state that an autonomous decision must be made: “1) intentionally, 2) with understanding, and 3) without controlling influences that determine their action”, and that factors 2 and 3 exist on a continuum that determines how autonomous a given decision is [1].

Faden et al. define informed consent as “an autonomous action by a subject or a patient that authorizes a professional either to involve the subject in research or to initiate a medical plan for the patient (or both)” [2]. Faden specifies that a person provides a valid informed consent “if a patient or subject with (1) substantial understanding and (2) in substantial absence of control by others (3) intentionally (4) authorizes a professional (to do I)”, where “I” is a given action [2]. If autonomous actions

exist on a continuum, then a person's informed consent also exists on a continuum [2]. Faden's definition outlines how fundamental informed consent is to modern medicine. Almost every patient encounter leads to a medical plan being initiated, ranging from risky procedures such as major surgery or bone marrow transplantation, to a routine follow-up physical examination being performed.

In practice, ensuring patient understanding has focused on ensuring that patients understand the risks and benefits associated with a treatment and the risks and benefits of not receiving a treatment. Physicians aim to ensure that patients understand this information in order to be able to make rational decisions that maximize their ability to achieve their goals. Physicians focus on explaining to patients the probability that an event (a specific risk or benefit) will occur, such as a surgery leading to a damaged ureter or an infection, or the surgery leading to a significant reduction in a patient's pain or improvement in their ability to mobilize [3]. Gigerenzer and Edwards argue that medical students and physicians should be educated on how to explain statistical risk information to their patients effectively [4]. It is essential to ensure that patients understand the probability of a benefit or an adverse event occurring or of their symptoms progressing without treatment to obtain an informed consent and to provide good medical care. Enhancing this understanding helps patients make informed decisions, as it ensures that they can make accurate epistemic predictions. However, this understanding is insufficient to make rational decisions. Physicians should ensure that patients also understand how a specific benefit or adverse event occurring, such as their symptoms worsening or new symptoms developing, will translate to changes in their emotional state and quality of life (QoL), as this understanding is just as important

to their decision-making process as understanding the probability that a specific outcome will occur. For example, a patient may comprehensively understand the probability of each risk of a procedure occurring, including the 50% chance of experiencing permanent incontinence. However, these probabilities are meaningless if they do not adequately understand how these particular adverse events (epistemic outcomes) will impact their QoL, the outcome that may be most important to them if they are thinking rationally and attempting to maximize their overall well-being. If, for example, incontinence typically lowers a patient's QoL by 8 points on a 10-point scale, this information would be extremely important for the patient to understand in order to make a treatment decision that best allows them to achieve their life goals. If they were to consent to a treatment based on a prediction that their QoL will only be lowered by 1 point on a 10-point scale, they are drastically undervaluing the effect of incontinence on their QoL and they misunderstand the impact this treatment may have on their life and cannot provide a valid informed consent. Clinicians and researchers should be concerned that healthy subjects and patients have been found to be poor predictors of the QoL ratings of others living with disease and of how their own QoL and emotional state will be impacted by future events. These inaccurate expectations may contribute to a significant misunderstanding that could be argued to impair a patient's ability to provide an informed consent. The following sections will examine research evaluating people's ability to predict their future emotional states, the current QoL of others, and their own future QoL.

Affective Forecasting, the Disability Paradox and Medicine

When healthy subjects are asked to rate measures of the QoL of those living with a variety of disabilities and illnesses, they often provide lower ratings than those living with the disability [5-8]. This phenomenon, which has been reproduced in many studies, has been termed the “disability paradox” [9]. For example, rectal cancer patients with a colostomy have been found to assign a higher value to a hypothetical life lived with a colostomy compared to healthy subjects and rectal cancer patients that did not have a colostomy [5]. Healthy women rate the health of breast cancer patients lower than the patients themselves [6]. Dialysis patients score the QoL of subjects in hypothetical scenarios involving dialysis higher than healthy subjects [7]. This phenomenon is believed to not simply be due to scale recalibration by individuals with a disability, but to be caused by the inaccurate predictions of healthy individuals themselves [9, 10]. People have not only been found to be poor predictors of the QoL of others who are living with a variety of illnesses and disabilities, they have also been found to be poor predictors of their own emotional reactions to a variety of events and their own future QoL [11, 12]. These predictions of their own emotional responses to future events, termed affective forecasts, are important in everyday decision-making and patients’ treatment decisions [10, 11].

These predictions are fundamental to standard models of rational decision-making. They may bear on many decisions outside laboratory settings, as when persons consider their options prior to making a choice, their expectations or beliefs regarding which option will maximize their happiness may be used in order to come to a

decision. These expectations may consciously or subconsciously be based on predictions of how each option will impact their emotions (affective forecasts), which may underpin their choices [13]. For example, if a person is trying to maximize pleasure, choosing between purchasing a popsicle at a near-by convenience store and driving for 15 minutes to purchase their favourite gourmet ice cream, their final choice may be based on which option they believe will maximize their happiness. This belief may be based on a subconscious prediction of how satisfied they will be with the convenient but sub-par snack compared to travelling for the premium treat. This prediction along with other factors should underlie this individual's final choice. Studies suggest that many people are poor at predicting the satisfaction or discontent that they will experience due to a future event, and this seems to be true based on individual experience [14]. People often make decisions to pursue an activity that they think will make them very happy, only to find out that after finishing the activity they are less happy than they initially predicted they would be. Studies have shown that people consistently overestimate their emotional response (happiness or sadness) to significant future events, including college dormitory placement, relationship dissolution, and tenure denial [14, 15]. For example, Dunn et al. identified that first-year college students who were assigned to "desirable" and "undesirable" college housing significantly over- and underestimated how happy they would be one year following their housing assignments respectively [16]. This overestimation of predicted emotional reactions to future events has been termed the impact bias [17]. This overestimation can be due to an incorrect prediction of the intensity of the experienced emotion or its duration [11]. These forecasting errors, if they map to expectations and occur in high-stake settings, can have important effects

on important life decisions, including medical decisions, where they may limit a patient's ability to provide a valid informed consent.

Before we discuss how affective forecasting errors can impact medical decision-making and the informed consent process, we must discuss one important caveat concerning affective forecasting research. In research, subjects predict emotional responses using numerical values to score an emotional reaction. In real-life situations, people do not quantitatively predict their emotional reactions prior to making a decision, and they may not consciously predict their future emotions before they make a decision at all. In our example above, our ice-cream fan did not quantitatively predict that the premium ice-cream would lead to a 9/10 experience of happiness, and they may not have even consciously thought of how happy they would be when eating it. However, tacit predictions or expectations may be embedded in individuals' thought processes and perceptions, which may inform their decisions if they are rational utility maximizers. For example, evidence suggests that a subject's anticipated regret can predict various health behaviours [18]. Although individuals are likely not true utility maximizers in their decision-making, improving the accuracy of individuals' subconscious predictions of their future emotional states and therefore their conscious expectations, may allow them to make decisions that better allow them to achieve their goals.

Before advancing further in our discussion of how affective forecasts and the impact bias can impact patients' decision-making, we will briefly outline some contributors to the impact bias, the tendency of individuals to overestimate their

emotional responses to future events, that have been outlined in the literature, and we will define some key terms that are important to understanding the impact bias.

Contributors to the Impact Bias

In our discussion, it is important to differentiate a “future event”, which we will define as the actual event that occurs in the future, from a “predicted event”, which is what the person making a prediction imagines the future event will be. The first contributor to the impact bias involves a difference between a predicted event and the future event itself. In our discussion, we will also differentiate an “actual emotional response”, the emotional reaction a subject experiences in response to a future event, from a “predicted emotional response”, the emotional response that a subject predicts they will have to a predicted event. We define the accuracy of an affective forecast as the difference between the predicted emotional response and the actual emotional response. We will now outline four potential contributors to the impact bias.

1) Failure to understand or predict an experience

If a subject inaccurately predicts what a future event will be, meaning the predicted event is very different from the future event, their predicted emotional response to the event may be different from their actual emotional response. For example, if a subject is asked to predict their emotional response to receiving a slice of cake, they may imagine a fresh slice from their favourite local bakery. They may predict that they will experience a substantial amount of joy. However, if the following day they

are given a slice of week-old cake, they might experience little joy and not even eat it. This difference between their predicted emotional response and their actual emotional response is due to the difference between the predicted and the experienced future event, as described by Gilbert and Wilson [19]. If a subject is a perfect predictor of a future event, the predicted event they imagine will be identical to the future event itself. Their predicted emotional response will be the emotional response that a subject predicts they will have to the future event, and this first contributor to the impact bias will be eliminated.

2) Focalism

Willson et al. define *focalism* as occurring when "people think too much about the focal event and fail to consider the consequences of other events that are likely to occur" [20]. Focalism can also contribute to impact bias. For example, if a subject is asked to predict their emotions several hours after winning a cash prize or receiving a parking ticket, they may not consider how the other events that occur throughout the day will impact their future emotional state, such as receiving negative feedback at the workplace or making a new friend. Wilson et al. identified focalism as a contributor to affective forecasting errors in college students' predictions of their emotional response to their school football team's performance, and they noted that forecasts could be improved by focusing subjects on their usual daily activities through the use of a "diary questionnaire" [20]. Other researchers have also identified focalism as a potential contributor to the impact bias in experiments where they demonstrated that a defocusing procedure (listening to a description of the daily life of the individual whose

emotions they would predict) led to less extreme positive and negative emotional forecasts [21].

3) Immune Neglect

Another contributor to impact bias is *immune neglect*, defined as not adequately accounting for the magnitude of one's ability to limit negative emotions through a variety of coping strategies [15]. If subjects do not adequately account for their inherent ability to limit their negative emotions, they will not accurately predict how their emotions will change with time [13]. This phenomenon was shown in several experiments by Gilbert et al., including college students' predictions of their emotional responses to a relationship ending and professors predicting their emotional responses to not receiving tenure [13].

4) Adaptation

The final contributor to impact bias that will be discussed is a subject's failure to consider how their values, goals and the activities from which they derive joy will change following an experience [9]. For example, if a subject were to predict their emotional response to their favourite television series being cancelled, they might fail to consider how they would adapt to this change and perhaps find a new hobby or series that they would equally enjoy. Ubel, Loewenstein, and Jepson demonstrated that failure to predict adaptation to the development of a disability can impact QoL predictions, by showing that exercises that lead participants to consider possible adaptation lead

subjects to provide less negative predictions of the QoL of those living with a chronic disability [22].

The Impact Bias in Medicine

As outlined above, people's predictions, the quantifiable ratings that they provide in the research context, of their future emotional states are susceptible to forecasting biases, which may impact their everyday decision-making. In the clinical context, the impact bias may significantly affect patient decision-making. If patients' predictions of their future emotional states are biased, their QoL predictions will be impacted, as emotional well-being is one of the many components of an individual's QoL, and their expectations or conscious beliefs regarding their likely future QoL will be affected, as these expectations may be based on subconscious QoL predictions. Patients considering multiple treatment options may consciously or subconsciously base their treatment decisions on what they predict their QoL and lifespan will be if they choose each treatment [23, 24]. Their treatment decisions may therefore be impacted by biased affective forecasts and QoL predictions. Several recent studies have examined how affective forecasting biases impact patients' and healthy individuals' QoL predictions in the clinical context [12, 25]. For example, patients awaiting kidney transplantation were found to predict a significantly larger increase in their QoL after transplantation than they reported experiencing after their transplant actually occurred, and healthy subjects have been found to score the average mood of patients on hemodialysis significantly lower than patients themselves [12]. A review by Halpern and

Arnold provides several examples of how focalism, immune neglect, and failure to anticipate adaptation can affect patient decision-making in the clinical context [10].

Consider a patient who has been recently diagnosed with a chronic illness and who was previously healthy. Their opinions regarding their future QoL might be impacted by the discrepancy between the QoL experienced by those with an illness and the general healthy public's perception of their QoL, the disability paradox, and affective forecasting biases. Their expectations regarding their QoL are based on how their symptoms might progress and affect their functioning and emotional well-being, which requires an understanding of each proposed treatment's efficacy and the natural course of their illness [24]. Importantly, these patients must make several predictions, not all of which are affective forecasts. They must predict whether a particular event will occur (for example whether their disease will worsen, or whether they will lose their ability to ambulate or function in a work environment), and they must predict what their emotional response will be to these events if they do occur. We will primarily focus on the latter, their affective forecasts, but the former, their epistemic forecasts, are also of importance in medical decision-making and have been the traditional focus of discussions aimed at improving patient understanding and their ability to make informed decisions. Patients' predictions of their emotional responses to the development of new symptoms and potential physical and functional limitations are susceptible to the forecasting biases we have identified above: focalism, immune neglect, and failure to predict adaptation. We will now focus on a specific clinical example in order to identify how these three forecasting biases may affect a patient's thought process.

The Impact Bias: A Clinical Case

Imagine a patient who has just been diagnosed with a chronic disease. This patient is provided with several potential treatment options, which include non-treatment. They will take many factors into account when making their treatment decision, which may consciously or subconsciously include their predicted future QoL if they choose each option. These QoL predictions will be based on how their disease's progression will impact their functioning and emotional responses [10]. These predictions involve epistemic forecasts (predicting whether their disease will progress and the likelihood of each symptom developing) and affective forecasts. For example, they may have to predict the likelihood of losing their mobility and how losing their mobility will impact their emotional well-being. We will focus on the latter, their affective forecasts.

This patient's affective forecasts are susceptible to the biases mentioned above. This patient's forecast may be affected by focalism. For example, they may understand that their mobility will be impaired in the coming years, and base their prediction entirely on their inability to enjoy activities that require ambulation, such as their love of jogging, while ignoring that many of their other favourite daily activities, such as reading, will be unaffected by their new disability. If they exhibit this enhanced focus on the parts of their life that will change and ignore those that will remain the same, they may make a QoL prediction that is significantly more negative than they would otherwise make and that may not be representative of their true future QoL. Immune neglect can also impact their predictions. For example, they may not account

for their coping mechanisms that will allow them to overcome their initial depression when they lose their mobility. Finally, they may fail to predict their adaptation to their new functional impairments. Perhaps they will develop a new hobby that does not require independent ambulation once they lose this ability, such as a newfound love for writing, reading or music. All of these biases can contribute to this patient's inaccurate prediction of their future emotional state and QoL, which may lead them to choose a management option that does not lead to their personal optimal outcome. For example, this patient may choose an extremely aggressive therapy, putting them at significant risk of serious adverse events due to a significantly inaccurate expectation of what their future QoL would have been if they had chosen a less aggressive treatment option.

Physicians should be concerned by the potential for patients' forecasting biases to prevent them from making medical decisions that align with their unique goals and values. Halpern argues that "patients need to be able to form realistic beliefs about their future QoL to make adequately informed decisions" [10]. If patients' affective forecasts and QoL predictions and therefore their expectations regarding their likely future QoL are un-realistic and inaccurate, then some may argue that they are therefore unable to make an informed decision and to provide a valid informed consent, which as we have outlined requires sufficient understanding [10]. If affective forecasting biases can impair patient understanding and render patients' treatment decisions non-autonomous, healthcare practitioners must be able to recognize when patients' decisions are significantly impacted by these biases and, if possible, help their patients improve the accuracy of their expectations, as will be discussed in chapter 4 [26]. Identifying when decisions are rendered non-autonomous due to affective forecasting biases is likely to

be a significant challenge for clinicians due to the difficulty in determining if a decision is being significantly swayed by these biases [26].

The Impact Bias and Clinical Trial Enrolment

In addition to concerns regarding the ability of the impact bias to impair patient understanding in the clinical context and to render their treatment decisions non-autonomous, the ability of these biases to impact patient understanding is even more concerning in the research context. Patients who are offered the opportunity to enrol in a clinical trial examining a novel treatment must consider trial enrolment as they would the other options that are available to them. They must consider the risks and benefits of each of their available options, including participating in the trial, and they must predict the impact that each available treatment option will have on their diseases course and on their future emotional state and QoL. These predictions are susceptible to the errors in judgement that we have mentioned, and patients may make clinical trial enrolment decisions based on inaccurate expectations of what their future QoL will be if they do not enrol and receive standard care or if they enrol and receive an experimental treatment. The impact bias' potential ability to affect the accuracy of patients' QoL predictions may significantly impair patient understanding and render their consent to enter a clinical trial non-autonomous.

The impact bias' ability to render patients' clinical trial enrolment decisions non-autonomous is particularly concerning compared to in the clinical context for several reasons. In the clinical context, patients and their physicians have overlapping goals.

They both aim to optimize the patient's health outcomes and well-being. In research, patients and study investigators might have differing primary aims. Patients often choose to enrol, as they believe they have a higher chance of improving their health in a clinical trial compared to receiving standard care, which might not be true, as patients who receive novel treatments may be worse off than those who receive placebo, who themselves may be worse off than those who refuse to participate altogether [27-29]. The primary goal of investigators is to generate knowledge, not to improve the health of each individual patient. It is concerning if investigators recruit patients in order to generate knowledge while patients themselves base their enrolment decisions on a misunderstanding of how their QoL will be impacted by trial participation compared to standard care. In this context, researchers may be argued to be taking advantage of patient misunderstanding in order to achieve their own aims. In addition, in the clinical context, all treatment options that are provided to a patient to choose from are believed to be beneficial to that patient. Some may have more risks than others but are more efficacious while others have less side effects but a lower chance of being effective. Nonetheless, all options made available to patients in the clinical context are believed to be beneficial to the patient. Patients who make a decision in the clinical context based on a misunderstanding of what their future QoL is likely to be are therefore still making a decision that is believed to be beneficial to their health and well-being. In clinical research, participants consent to receive treatments that may cause substantial harm and that have not yet proven to provide any clinical benefit [27, 30]. Participants may enrol in a trial and receive an experimental treatment that will prove to not be beneficial and that may be found to worsen patients' health outcomes based on a

misunderstanding, which is concerning. Finally, the ability of the impact bias to cause patients to consent to participate in a clinical trial based on a misunderstanding is particularly concerning, as the knowledge generated from these trials is built upon patient misunderstanding. In the clinical context, a patient's forecasting biases and the treatment decisions they may make based on a misunderstanding only impact themselves and their family. In research, their decisions ultimately contribute to scientific knowledge and society as a whole. Society benefiting from knowledge generated based on the misunderstandings of vulnerable members of the community raises troubling ethical questions. It seems morally wrong for society and science to benefit from subjects agreeing to enrol in trials based on mistaken beliefs regarding their own QoL when participation might not benefit them in any way and may be harmful. In addition to these ethical questions, conducting trials based on patient misunderstanding has practical consequences. It may erode the public's trust in the scientific community. This may impair patient recruitment in future trials or the public's acceptance of interventions endorsed by the scientific community, such as routine immunization.

Conclusion

In conclusion, in order to provide a valid informed consent to participate in a clinical trial, research participants must have an adequate understanding of numerous aspects of clinical trial participation. This understanding should include a reasonably accurate understanding of what their QoL is likely to be if they do not participate in a

clinical trial and receive standard clinical care and how their QoL would be impacted by clinical trial participation. As we have seen, people have been shown to be poor predictors of their future emotional states and their future QoL. This is concerning, as if patients have a poor understanding of what their future QoL is likely to be as their disease progresses and they develop new symptoms, it may be argued that they cannot provide a valid informed consent to participate in a clinical trial. In the next chapters we will outline research in the field of autoimmune diseases and identify some key challenges in this field relating to affective forecasting, we will outline a novel research protocol that has been developed to determine if patients with autoimmune diseases make accurate predictions regarding what their future QoL is likely to be if they receive standard clinical care and if these predictions impact their clinical trial enrolment decisions, and finally, we will evaluate the potential implications of this research.

Chapter 2:

Preventing the Development and Progression of Chronic Autoimmune Disease: Successes, Challenges, and the Impact Bias

Introduction

As outlined in chapter 1, in order to provide a valid informed consent a research participant must have an adequate understanding of trial participation. They must understand numerous aspects of the clinical trial and how their life will be impacted by participating as compared to declining to participate. In order to understand this difference, patients must understand how their life will be impacted by their illness, which may progress as they receive standard treatment outside of a clinical trial. This involves understanding how their QoL may change with time and how their emotional state will be impacted by the progression of their illness. This may involve conscious or subconscious predictions of their future emotional states that may be susceptible to the impact bias. The impact bias' potential effect on patients' affective forecasts and QoL predictions and therefore their understanding, decision-making, and ability to provide an informed consent to enrol in a clinical trial is particularly concerning in autoimmune disease research.

In recent decades, novel treatments have been developed and approved for a variety of chronic autoimmune conditions, and in several autoimmune illnesses the belief that patient outcomes can be improved by early treatment with disease-modifying agents has become accepted [31, 32]. Many treatments are currently being developed

and have been recently examined in clinical trials with the aim of slowing or stopping the progression of these illnesses or preventing their onset (see Table 1). Many of these therapies involve powerful agents or treatment protocols that have the ability to cause severe side effects and some have a non-trivial mortality risk [33]. Due to these non-trivial risks, it is important that all patients enrolling in clinical trials have a strong understanding in order to provide a valid informed consent. A strong understanding should include a reasonably accurate expectation of what their future QoL will be if they do not enrol in a potentially risky clinical trial and receive standard clinical care in order to ensure that patients' trial enrolment decisions are not based on a misunderstanding of what their future QoL is likely to be. This is particularly concerning in chronic autoimmune disease research, as the chronic nature of these illnesses may lead to the accumulation of symptoms and progressive disability with time. The belief that the progression of these illnesses may be delayed or stopped if patients are treated early in their disease course has led to trials that recruit patients soon after their diagnosis and in some illnesses prior to them receiving a confirmed diagnosis or developing clinical symptoms. Recently diagnosed patients and patients that have not yet developed symptoms of their chronic autoimmune disease should understand how their QoL is likely to be impacted by their disease's progression in order to provide a valid informed consent. This understanding may be limited as they may have limited/no experience living with their illness and their expectations about their future QoL may be susceptible to impact bias.

In this chapter, we will review the burden of several autoimmune diseases and recent investigational interventions involving aggressive therapies shortly after onset.

We close by examining concerns relating to the impact bias associated with the trials that have been performed and may be likely to be proposed in the coming years and outlining how concerns relating to affective forecasting biases are not isolated to the field of autoimmune disease research.

Burden of Autoimmune Diseases

Autoimmune diseases are relatively common and are estimated to affect 4.5% of the general population [34]. Estimates suggest that approximately 93 500 Canadians have received a multiple sclerosis (MS) diagnosis and 270 000 Canadians have inflammatory bowel disease (IBD), and Canada is believed to have one of the highest prevalences of MS and IBD worldwide [35, 36]. The incidence rates of autoimmune diseases such as MS, type 1 diabetes (T1D), and IBD are increasing [37-39]. This trend is not fully understood, but changing environmental factors are thought to play a role [39]. This increase in autoimmune disease incidence represents a growing concern and has led to the conduct of many trials aimed at treating and preventing the onset of these diseases.

Emerging Autoimmune Disease Treatment Paradigms

Research into treating these diseases aims to inhibit the specific process that leads to autoimmunity while preserving the functionality of the body's physiologic immune responses [38]. In recent decades, research has led to the development and

clinical availability of powerful disease-modifying treatments, such as monoclonal antibodies, and has expanded treatment options and improved patient outcomes for a variety of autoimmune diseases, including IBD, rheumatoid arthritis (RA), and MS [40-44]. Researchers have also examined “resetting” patients’ immune systems by conditioning/ablating their existing immune systems and then performing autologous hematopoietic stem cell transplantation (AHSCT) in MS, IBD, RA, and T1D [33, 45-47]. Some of these powerful agents and treatment protocols have broad effects on a patient’s immune system and are associated with severe side effects, including elevating a patient’s risk of developing a malignancy and serious infections [38, 43, 48, 49]. These treatments may reduce patients’ symptoms and improve their QoL, but a cure for IBD, RA, T1D, and MS remains elusive.

Identifying and Treating Preclinical Patients with Autoimmune Diseases

Early treatment of autoimmune diseases may improve patient outcomes by stopping the development/progression of autoimmunity before irreversible damage occurs [50, 51]. As irreversible end-organ damage and changes to a patient’s immune system may occur prior to disease diagnosis and potentially prior to symptom development, there has been an interest in developing methods to diagnose patients earlier in their disease course or prior to onset of clinical symptoms. This has led to changes in the diagnostic criteria of certain diseases, such as the McDonald criteria in MS, and the identification of markers that may be used to identify patients at high-risk of developing a disease [52-56].

While some studies aimed at preventing disease development and progression have shown evidence of clinical benefit, a cure to these illnesses has not been identified. Furthermore, the treatments being examined to prevent disease development and irreversible end-organ damage vary in their risks, from relatively benign (oral insulin) to hazardous (AHSCT), raising several concerns [57, 58]. We will now briefly review research examining the treatment of patients with three common autoimmune diseases; multiple sclerosis, rheumatoid arthritis, and type 1 diabetes, three illnesses with differing symptoms, treatments, and research trajectories, where investigators have attempted to identify patients early on in their disease course in order to treat them with immune-modulating treatments with varying levels of success. We will also outline researchers' ability to identify patients at risk of developing these illnesses and research examining the efficacy of treatments that aim to prevent disease development in these patients.

Multiple Sclerosis

MS is an autoimmune disease characterized by an immune response against white matter within the central nervous system leading to axonal demyelination, which leads to symptomatic episodes of neurologic symptoms including weakness and sensory changes that characterize the most common relapsing-remitting form of MS [43, 59-61]. Often, after one to two decades, patients develop progressive symptoms that impair their functioning and may lead to severe disability, and it has been estimated that patients with MS generally have a 7-14 year reduction in life expectancy [60, 62].

Immune-Modulating Therapy

Evidence suggests that MS should be treated early on in the disease process with one of several available disease-modifying treatments [31]. A variety of therapies that utilize different mechanisms of action to impact the immune system have been found to reduce relapse rates in patients with relapsing-remitting multiple sclerosis (RRMS) and are now available, providing patients and clinicians with numerous treatment options [63]. Monoclonal antibodies that have been found to reduce relapse rates in patients with MS in randomized controlled trials include natalizumab, which binds to integrin proteins and prevents inflammatory cell migration, alemtuzumab, an antibody that targets CD52, and ocrelizumab, an antibody that targets CD20 expressing cells [63-67]. These agents are some of the most effective available therapies [43, 68]. However, none of them completely prevent relapse emphasizing the need for further research to identify novel treatments to improve patient outcomes [63]. For example, in the OPERA 1 trial, the annualized relapse rate in patients receiving ocrelizumab was 0.16 compared to 0.29 in those receiving interferon-beta [66]. In addition, the most effective MS treatments are associated with a greater risk of experiencing a significant adverse event [43]. For example, a recent report identified several deaths that may have been related to alemtuzumab treatment [69]. Two treatment strategies have emerged due to the higher risk associated with the more effective therapies; the “escalation” strategy and the “induction” or “early intensive” strategy [43, 68, 70]. The escalation strategy involves starting treatment with one of the safer medications and switching patients to a more effective medication only when the current treatment fails, whereas the induction strategy involves starting patients initially on the more effective

treatments [43, 68, 70]. Two clinical trials that aim to determine which treatment strategy is superior are currently recruiting [70-72]. Other treatments, such as ublituximab and ofatumumab, two additional antibodies that target CD20 expressing cells, similar to ocrelizumab, are also being examined in clinical trials in order to determine if they improve patient outcomes [70, 73, 74]. These agents' efficacies are being evaluated in patients with RRMS and an Expanded Disability Status Scale (EDSS) score equal to or less than 5.5 (the less significantly disabled half of the scale) [70, 73, 74].

Studies have examined the use of AHSCT in patients with MS who have relapsed despite disease-modifying therapy [33]. A phase 2 single-group trial found that none of the 23 participants that survived transplantation had a relapse in 179 patient-years following transplant [75]. However, one patient died during the trial, which caused the investigators to change the protocol [75]. A randomized trial comparing AHSCT to disease-modifying treatments found that 6% of participants that underwent AHSCT and 60% of participants that received disease-modifying therapy had a clinical relapse with a median follow-up of 2 years [33, 76]. Further research will need to be done in order to optimize stem cell transplantation protocols in MS, and to directly compare the efficacy of this treatment with specific treatment options. One such trial is currently underway comparing AHSCT and alemtuzumab treatment that has a primary completion date of 2022 [77].

Preventing MS Development

As evidence suggests MS should be treated early on in the disease course to optimize patient outcomes, the McDonald diagnostic criteria have been updated to allow

for earlier diagnosis and treatment [78]. Recent evidence also suggests that MS has a prodromal phase, which if accurately identified may allow treatment to be initiated prior to symptom onset [79]. Prior to receiving a MS diagnosis, patients may be diagnosed with two syndromes that often continue to develop and progress to a confirmed MS diagnosis: clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS) [80]. Lublin et al. define CIS as “the first clinical presentation of a disease that shows characteristics of inflammatory demyelination that could be MS, but has yet to fulfill criteria of dissemination in time” and RIS as when the “incidental imaging findings suggest inflammatory demyelination in the absence of clinical signs or symptoms” [81]. Estimates of the rate of progression from these two syndromes to a diagnosis of MS vary, with estimates of the rate of CIS developing into MS ranging from 42-82% [80, 82]. Treating patients with these syndromes may slow disease progression (the time to receive a confirmed MS diagnosis), and may be more effective in improving long-term patient outcomes than treating patients once they have a confirmed diagnosis of MS and irreversible damage to their nervous system or irreversible changes to their immune system may have already occurred [82, 83]. Interferon-beta, glatiramer acetate, cladribine, teriflunomide and minocycline have been found to help delay the progression from CIS to a confirmed MS diagnosis, with some showing only a short-term benefit, however the diagnostic criteria for MS have changed and some patients in these studies would have been diagnosed with confirmed MS if the current criteria were used [83]. It is possible that powerful riskier agents such as alemtuzumab, which have been found to be the most effective agents in treating patients with MS, may be more effective in prolonging the time to progress from CIS and RIS to MS than the agents that have

already been evaluated in trials. However, using agents that have more severe side effect profiles in individuals with CIS, who may never go on to develop a confirmed diagnosis of MS is concerning. Future research may identify factors that help predict which patients with CIS and RIS are at the highest risk of progressing to MS and most likely to benefit from treatment. This may help address concerns that treating patients with CIS will lead to increased healthcare costs and potentially significant lifestyle changes in otherwise healthy patients who may never go on to progress to a confirmed MS diagnosis [83]. Future studies may also identify individuals in the prodromal phase of MS or those at high-risk of developing MS prior to their first clinical episode and diagnosis with CIS or RIS, which may further improve patient outcomes by allowing treatment even earlier in the disease process. One trial currently underway is examining the ability of dimethyl fumarate to delay symptom onset in patients with RIS, which may identify a means of improving patient outcomes by acting before symptom onset during the prodromal phase of MS [84].

As clinicians' ability to identify patients with prodromal MS who are at high risk of progressing and patients who have recently developed MS symptoms but have not yet failed standard therapies but are at highest risk of experiencing severe disease improves, riskier therapies such as AHSCT may start to be tested in these patient populations. This is concerning as these patients may have a poor understanding of what their future QoL is likely to be.

Rheumatoid Arthritis

RA is a chronic autoimmune disease that primarily impacts patients' joints, leading to pain, joint destruction, and disability [44]. However, RA also has systemic manifestations, including lung and vascular involvement leading to an elevated mortality risk [44, 85].

Immune-Modulating Therapy

RA should be treated aggressively with disease-modifying antirheumatic drugs (DMARDs) as early as possible in the disease's course [86]. In one meta-analysis, patients who were treated with a DMARD soon after their diagnosis had better responses to their treatment [86-89]. Several other studies have shown that early treatment can improve patient functioning, lead to disease remission, and reduce radiologic progression [90]. Clinicians have many therapeutic options at their disposal, including methotrexate, hyroxychloroquine and biologic agents such as adalimumab, etanercept and rituximab. Treatment advances have led to the proportion of patients with RA that achieve disease remission increasing [44, 91]. In fact, a phase 3 trial that examined the efficacy of stem cell transplantation and methotrexate therapy, the ASTIRA trial, was not completed due to minimal recruitment, which Snowden and colleagues state was due to the common use of effective biologic agents [92]. However, despite treatment advances, not all patients achieve complete remission and many patients' positive responses diminish with time [44]. Research is needed to identify effective treatments for these refractory patients [44]. One such study, examining the

efficacy of olokizumab a monoclonal antibody that targets interleukin-6, in patients who have not responded adequately to TNF inhibitor (ex: adalimumab) treatment is underway and currently recruiting patients [93, 94].

Preventing RA Development

Several studies have examined the prevention of RA in patients at risk of developing RA [86]. Studies have tested the ability of several therapies to prevent the progression of inflammatory arthritis, a condition that is thought to be a precursor to the development of RA (symptoms that do not yet meet all of the criteria that are required for a clinician to diagnose RA), into RA [86]. For example, the PROMPT study found that methotrexate treatment reduced the proportion of patients that developed RA within 30 months compared to placebo (22/55 in the methotrexate group versus 29/55 in the placebo group), and the ADJUST study found that abatacept treatment reduced the proportion of patients that developed RA within a year (12/26 in the abatacept group versus 16/24 in the placebo group), however, neither of these changes were found to be significantly different [86, 95, 96]. Based on these studies, it is possible that these treatments will have a role in preventing RA onset, however, their effect seems to be limited and will not provide patients with a promising treatment that will consistently stop their disease from progressing.

Other studies have assessed the ability of therapies to prevent the development of RA in patients that test positive for markers, such as antibodies to citrullinated protein/peptide antigens (ACPA), that are associated with the development of RA prior to symptom onset [55, 86, 97]. One study examining the ability of rituximab to prevent

disease onset in patients who tested positive for ACPA found no statistically significant difference in the proportion of patients that developed arthritis between the rituximab and the placebo treated groups [55]. However, rituximab treatment was found to delay arthritis onset [55]. Other studies are currently underway, including the StopRA trial, which is testing the ability of hydroxychloroquine to prevent the development of RA in patients that test positive for anti-CCP3, a marker that is predictive of the future development of RA [98]. Hydroxychloroquine is believed to be one of the safer drugs used to treat RA, therefore, it would be an attractive option to clinicians and patients if it is found to prevent the development of disease [99]. However, despite its relative safety compared to other treatment options, it is associated with side effects such as QT interval prolongation, which can lead to the development of a fatal arrhythmia [100]. Future trials may test the ability of other agents, which may have more severe adverse effect profiles, to stop RA onset in patients at risk of its development, and will potentially identify patient subgroups that have the highest chances of benefiting from these treatments to optimize patient outcomes.

Type 1 Diabetes

T1D is a chronic disease defined by autoimmune pancreatic beta-cell destruction, leading to impaired blood glucose regulation [101]. However, unlike in MS and RA, the mainstay of treatment is insulin and insulin-based regimens and not agents that alter immune function to prevent autoimmune end-organ damage [101]. Insulin based regimens aim to maintain physiologic blood glucose concentrations, which has

been shown to reduce T1D cardiovascular and microvascular complications [101]. Optimal management requires multiple daily insulin injections or an insulin pump, however, despite available therapies, patients with T1D are estimated to live approximately 10 years less than a non-diabetic and are susceptible to many potential complications [101]. There is hope that in the coming years and decades automated insulin delivery systems will greatly improve patient management [101].

Immune-Modulating Therapy

At diabetes diagnosis, patients often have residual beta-cell function prior to complete beta-cell loss. Several studies have examined the ability of therapeutic agents that target the immune system to improve patient outcomes in patients who have been recently diagnosed with T1D, by preventing the autoimmune destruction of subjects' remaining beta-cells [102]. Cyclosporin, the first immunosuppressant tested in this context, was found to decrease patients' short-term insulin requirements, however, it did not lead to long-term disease remission [102-104]. Several monoclonal antibodies have similarly been tested in recently diagnosed type-1 diabetics [102]. Teplizumab therapy was compared to placebo in the PROTÉGÉ trial [105]. After 2 years of follow-up, teplizumab therapy did not significantly improve patients' HbA1C levels compared to baseline, however, a higher proportion of subjects treated with teplizumab were found to have an HbA1C below 7% [105]. After 2 years of follow-up, 3 of the 207 patients that were treated with teplizumab were not receiving insulin treatment, compared to 0 out of the 98 patients that were treated with placebo [105]. Rituximab treatment has also been examined, but has not been found to have a persistent benefit [102, 106]. The ability of

many other agents to improve clinical outcomes in patients with T1D have been examined, as outlined in the 2019 review by Greenbaum et al., however, no agent has been identified that can consistently prevent T1D progression [107].

Researchers have also examined the impact of AHSCT in recently diagnosed type-1 diabetics using several protocols [108]. Voltarelli et al. completed the first study examining this treatment, which found that 21 of the 25 subjects examined did not require insulin following their transplant, with later follow up studies finding that 11 subjects did not require insulin treatment for >= 3.5 years [45, 108, 109]. At the time of Malgremim et al.'s 2017 publication, 3 patients who underwent this transplantation protocol were not requiring insulin therapy [109]. This powerful treatment regimen seems to be effective in the few trials that have been completed in a limited number of patients in a select group, however, as noted above despite early periods where subjects no longer require insulin, most patients treated with this regimen eventually continue to progress and need insulin therapy. Penaforte-Saboia and colleagues examined whether patients treated with these regimens have better clinical outcomes compared to subjects receiving standard care in Brazil, and found that those treated with stem cell transplantation had 0 microvascular complications compared to 21.5% of patients receiving standard care (following a median follow-up of 8 years post-diagnosis) [108, 110]. This study matched patients for comparison of the two groups, however, its retrospective nature makes it difficult to determine if the observed effect is solely due to the stem cell therapy protocol [110]. This powerful treatment regimen is not without risks, for example in a Polish study examining a similar protocol, one patient died from sepsis [49, 108]. This research group notes that the conditioning regimen

used has a higher mortality rate than diabetes itself, which raises ethical concerns regarding its use [49]. Further trials will likely need to find a safer alternative that is effective before a majority of patients who have been recently diagnosed with T1D are willing to consent to this therapy.

Preventing T1D Development

As mentioned earlier, researchers can now identify patients that are at high-risk of developing T1D based on a variety of factors, including the presence of certain antibodies, glucose tolerance and other patient characteristics [52-54, 111]. Certain autoantibodies can be very predictive of T1D development. Studies have found that in a specific patient population the presence of three autoantibodies gives subjects a 100% risk of developing T1D in a 5 year span and that children with at least 2 autoantibodies have an 84% chance of developing T1D by adulthood [52, 101, 111]. In a study of Finnish children, all children that were positive for both glutamic acid decarboxylase antibodies (GADA) and insulinoma-associated protein 2 autoantibody (IA-2A) went on to develop T1D [112]. Studies have examined the ability of dietary interventions (nicotinamide), antigen therapies (nasal and oral insulin), and immunomodulatory agents to prevent the development of diabetes in these patients prior to them developing symptoms and receiving a clinical diagnosis, and several trials are currently underway [107]. However, in this patient population as well, no agent has been identified that has a lasting ability in large randomized controlled trials to stop disease progression [107].

Affective Forecasting and Chronic Autoimmune Disease Research

As outlined above, numerous studies have been conducted and are currently underway examining the efficacy of drugs that target the immune system and AHSCT to slow/prevent the progression of chronic autoimmune diseases and to prevent their development. These three diseases and the respective research into their treatment demonstrate different research paradigms that reflect the efficacy of available treatments and the changing treatment landscapes in each field. For example, in RA where DMARDs are generally effective, studies examining resetting individuals' immune systems with autologous transplantation could not complete recruitment as effective DMARDs emerged. A new trial proposing to perform AHSCT in recently diagnosed patients with RA whose illness has not yet demonstrated it is refractory to available treatments would likely not receive ethics approval. Whereas in T1D, where no treatments targeting the immune system have been shown to be able to prevent disease progression and pancreatic beta-cell destruction, researchers have recently performed AHSCT in newly diagnosed patients. In the coming years, powerful new therapies with the potential to cause severe adverse effects may be developed and tested in patients that have been recently diagnosed with chronic autoimmune illnesses. As our ability to predict who is at high-risk of developing severe chronic illnesses increases, studies may be proposed that aim to examine the ability of powerful and potentially risky therapies to prevent disease onset in such patients prior to symptom onset. These studies may recruit recently diagnosed, pre-symptomatic, and paediatric

patients, raising numerous ethical concerns, including two involving the consent process and the impact bias, which will be outlined in the following section.

Recently Diagnosed and Pre-clinical Patients: The Impact Bias and Trial Enrolment

Recently diagnosed and pre-symptomatic patients are potentially susceptible to the impact bias and may overestimate how their QoL will be negatively impacted by their disease's progression and development. Pre-clinical patients that have not experienced any symptoms may believe that the QoL of symptomatic patients who have been living with their illness for years is lower than affected patients report themselves, due to the disability paradox. Pre-clinical patients' expectations of their own future QoL, which may affect their enrolment decisions, may also be overly negative due to the impact bias. Similarly, recently diagnosed patients have little experience evaluating how their QoL will be impacted by their illness and may overestimate how it will be negatively impacted by its progression. These patients have little/no experience discovering how they will adapt to new symptoms and disabilities and to how their emotional immune system will help them avoid prolonged negative emotional states associated with their disease's progression. They may also be susceptible to focalism and only focus on how their illness will change their daily life and not on any of the aspects of their life that will remain the same and that they will still enjoy. In addition, these patients may be emotionally vulnerable, as they have recently received a potentially life-altering diagnosis. Nash suggests that patients undergo Kubbler-Ross's "stages of grief" (denial, anger, bargaining, depression and acceptance) when they receive a new medical diagnosis [113]. Patients that have been recently diagnosed with a severe chronic

autoimmune disease might struggle to accept their diagnosis, especially if they have not yet developed any symptoms and have been identified in a pre-clinical stage. They are particularly vulnerable throughout this process, especially in the bargaining stage where Nash describes they invest hope in postponing their diagnosis [113]. This emotional vulnerability may impact their QoL predictions and enrolment decisions.

Paediatric Clinical Trial Enrolment and the Impact Bias

Most of the trials outlined above recruited adult patients. However, in illnesses such as T1D whose incidence peaks in childhood and adolescence and other chronic autoimmune conditions that can develop in childhood and adolescence, such as paediatric MS, paediatric patients have been and will continue to be recruited into clinical trials [101]. Involving children in clinical research ensures that information on the safety and efficacy of medications in this unique population that can guide treatment decisions is obtained. Historically most clinical trials have recruited adults, so information on drug efficacy in children is limited [114, 115]. Despite the benefits and need for paediatric research these trials face unique concerns regarding informed consent, QoL predictions, and the impact bias.

Adult patients' predictions of their own future QoL may affect their enrolment decisions. In paediatric research, QoL prediction is further complicated by the fact that parents/guardians must consent to their child's enrolment, which may involve a more complex QoL prediction, as it involves predicting the future QoL of someone else. Parents/guardians must predict what their child's future goals and values will be, which may be more difficult than an adult patient's prediction of how their own goals and

values may change in the future. This may impact how they believe their child's disease's progression will affect their future emotional states and QoL.

In the context of T1D, parents/guardians may consider their child's current discomfort with regular insulin injections and the negative emotions their child may be experiencing due to their new illness, without adequately considering that as their child matures and develops, their discomfort with injections and their fear of being different from their peers may diminish. If they do not adequately consider the rapidly changing nature of children, the QoL they predict their child will have may be significantly different from the true QoL they will eventually experience. This may lead a parent/guardian to make an enrolment decision they would otherwise not have made. It may be argued that in diseases that develop in both adolescents and young adults that are not imminently life-threatening, if there is no significant reason to believe pathology differs between these two groups, then risky clinical trials should be conducted in those that are capable of consenting to their own enrolment to avoid this challenge. For example, trials examining the ability of AHSCT to prevent T1D progression in recently diagnosed patients should be conducted in adults.

Powerful Therapies to Treat Patients with Non-autoimmune Diseases Early on in their Disease Course

Autoimmune diseases are not the only diseases where physicians have examined utilizing powerful and potentially risky therapies early on in a patient's disease course in order to improve patient outcomes. For example, hematopoietic stem cell

transplantation has been performed in thousands of young patients with thalassemia and sickle cell disease and gene therapy has been proposed as a potential cure for many genetic illnesses, including sickle cell disease [116, 117]. Patients with chronic non-autoimmune diseases such as sickle cell disease or their decision-makers who are offered the opportunity to enrol in clinical trials evaluating potentially risky therapies must make enrolment decisions that are similar to those made by patients with autoimmune diseases. We will now briefly outline research evaluating potentially risky sickle cell disease treatments in order to demonstrate that patients in many fields of medicine are faced with difficult enrolment decisions where understanding how their QoL is likely to be affected if they do not enrol in a trial is crucial to making an informed enrolment decision.

Sickle Cell Disease

Sickle cell disease (SCD) is an inherited hemoglobinopathy that is caused by a mutation in the beta-globin subunit of haemoglobin that leads to the production of abnormal haemoglobin, Haemoglobin S (HbS) [118]. The properties of this abnormal haemoglobin lead affected patients' red blood cells to have altered functioning, which causes the many complications associated with this illness, including stroke, pulmonary hypertension, and renal failure [118]. Hydroxyurea is the only medication that is approved by the Food and Drug Administration (FDA) to treat SCD, which has been shown to reduce patients' morbidity and mortality, however, it is not a cure and SCD is known to be a particularly challenging disease to treat [117, 118].

Novel Treatment Strategies

Hematopoietic stem cell transplantation (HSCT) has emerged as a curative option for some patients with SCD [119]. Matched sibling donor transplantation in children with SCD is associated with good efficacy and low rates of graft-versus host disease, a severe potential complication of HSCT [119]. Patients that attain successful engraftment of donor stem cells no longer experience the vaso-occlusive damage that leads to the many complications of SCD [120]. However, matched sibling donors are not available to most patients with SCD [119]. Due to the limited availability of matched sibling donors, treatment alternatives are currently being evaluated in clinical trials (see Table 2). Haploidentical transplants have been evaluated in clinical trials in order to address the shortage of matched sibling donors. One such trial, evaluating the efficacy and safety of haploidentical stem cell transplantation in 8 SCD patients found that 3/8 patients attained successful engraftment while 2/8 patients passed away due to chronic graft-versus host disease complications [120]. A recent review by Bauer et al. outlines several other trials that are currently underway that aim to examine the use of HSCT in SCD patients [119].

Researchers are also exploring the use of gene therapies, including gene addition and gene editing approaches, to treat patients with SCD [121]. Gene therapies that utilize modified patient derived cells offer the promise of curing SCD in patients who do not have a matched sibling donor with an extremely low risk of causing graft-versus host disease or leading to transplant rejection [121]. However, gene therapies are associated with their own theoretical and clinically confirmed risks [122]. For example, certain gene therapy vectors that have been utilized have been found to cause leukemia

[119, 122]. Other vectors, which are believed to be safer than those that have been used previously, are currently being evaluated in phase 1 clinical trials in patients with SCD, as outlined by Demirci et al [121]. The safety of these approaches in SCD patients will be determined in these studies and patients that are offered the chance to participate in these and other similar trials must make a complicated enrolment decision, where their beliefs regarding what their future QoL is likely to be if they do not participate in the trial might play a significant role in their enrolment decisions.

Identifying Trials of Particular Concern due to the Impact Bias

As we have seen, affective forecasting errors may impact patients' clinical trial enrolment decisions and their ability to provide informed consent. Affective forecasting errors' ability to affect patient understanding is particularly concerning in specific circumstances, which are present in some of the trials that we have outlined above in autoimmune disease and SCD research, which when present should alert research review boards and study investigators to be mindful of this potential effect and to consider implementing measures, such as those that will be discussed in chapter 4, to ensure that patient understanding is adequate prior to trial enrolment.

The first condition in which affective forecasting errors may be concerning is in diseases with a chronic progressive course that are manageable with relatively safe medications, but nonetheless have an impact on patients' long-term health and QoL, such as T1D. In this circumstance, enrolling in a clinical trial requires one to have a reasonably accurate expectation regarding how one's QoL will be impacted by their

disease's progression over many years while receiving standard care. The second condition where affective forecasting errors may be concerning is in trials that evaluate the efficacy of potentially highly morbid treatments (AHSCT) or treatments that have outcomes that are highly uncertain (gene therapy or other novel treatments). In this circumstance, patients are agreeing to take on a high risk by participating and this decision should be based on a strong understanding of what their QoL is likely to be if they did not participate and received standard care. The third circumstance of concern is in trials that evaluate the efficacy of treatments in patients that have been recently diagnosed with their illness. Patients recruited into such trials have had little experience living with their illness and may be particularly susceptible to making affective forecasting errors that lead them to misestimate their likely future QoL as their disease progresses. Finally, the fourth circumstance in which potential affective forecasting errors are particularly concerning is in trials that evaluate the efficacy of aggressive and risky treatments that are likely to have a small survival advantage over standard care in patients with lethal illnesses and a limited remaining lifespan. Patients who enrol in such trials may misestimate the QoL that they will experience during their remaining lifespan, which may lead them to make enrolment decisions that they would otherwise not have made. This is concerning as patients with a limited remaining lifespan should be empowered to make decisions that optimize their remaining QoL. In summary, affective forecasting errors are particularly concerning in trials that evaluate treatments in chronic conditions that have somewhat effective available therapies, that test risky or highly morbid treatments, that recruit recently diagnosed patients, and that evaluate aggressive treatments that are likely to have a small survival advantage compared to

standard care. When these conditions are present, and in particular when multiple conditions are present simultaneously, investigators should consider how affective forecasting biases may impact patient decision-making and consider implementing measures to improve the accuracy of patients' QoL expectations in order to help them make rational decisions that allow them to achieve their goals.

Conclusion

As we have seen in chapter 1, patients' affective forecasts and future QoL predictions may be susceptible to the impact bias and may affect their clinical trial enrolment decisions. This is particularly concerning in the field of autoimmune disease research and in other disease areas, such as SCD, where patients who have been recently diagnosed with chronic illnesses or have been identified as being at high-risk of their development must consider what their future QoL will be when they are offered the chance to enrol in a potentially risky clinical trial and where patients that are refractory to existing therapies must choose between pursuing standard care or enrolling in a clinical trial examining a potentially risky treatment such as AHSCT. The following chapter will outline a research protocol that is currently underway that aims to determine whether patients that have been recently diagnosed with chronic autoimmune diseases make accurate predictions regarding their potential future QoL and if these predictions have an impact on their willingness to enrol in a risky clinical trial and their epistemic predictions.

Table 1: Recently conducted and ongoing trials evaluating the ability of immune-modulating and other powerful and potentially risky therapies to treat, prevent, and cure MS, T1D, RA.

Trial Name or Published Article Title (NCT ID)	Disease	Therapy	Status
RCT Comparing Autologous Hematopoietic Stem Cell Transplantation Versus Alemtuzumab in MS (RAM-MS) (NCT03477500)	MS	AHSCT vs. Alemtuzumab	Recruiting
Rituximab Versus Fumarate in Newly Diagnosed Multiple Sclerosis. (RIFUND-MS) (NCT02746744)	Early RRMS or CIS	Rituximab vs. Dimethyl fumarate	Active, not recruiting
Hydroxychloroquine in Individuals At-risk for Type 1 Diabetes Mellitus (TN-22) (NCT03428945)	Individuals at risk of developing T1D	Hydroxychloroquine	Recruiting
Recent-Onset Type 1 Diabetes Trial Evaluating Efficacy and Safety of Teplizumab (PROTECT) (NCT03875729)	Recently diagnosed T1D	Teplizumab	Active, not recruiting
Rituximab and Abatacept for Prevention or Reversal of Type 1 Diabetes (TN25) (NCT03929601)	Individuals at risk of developing T1D	Rituximab and Abatacept	Recruiting
C-peptide levels and insulin independence following autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus [58]	Recently diagnosed T1D	AHSCT	Completed
Strategy to Prevent the Onset of Clinically-Apparent Rheumatoid Arthritis (StopRA) (NCT02603146)	Individuals at risk of developing RA	Hydroxychloroquine	Recruiting

A Study to Compare Upadacitinib (ABT-494) Monotherapy to Methotrexate (MTX) Monotherapy in Adults With Rheumatoid Arthritis (RA) Who Have Not Previously Taken Methotrexate (SELECT-EARLY) (NCT02706873)	Methotrexate-naïve RA patients	Upadacitinib vs. Methotrexate	Active, not recruiting
Transplantation of Autologous Bone Marrow Derived Stem Cells in Patients With Rheumatoid Arthritis (NCT03067870)	RA	Autologous bone marrow-derived stem cell transplantation	Active, not recruiting

Table 2: Ongoing trials evaluating the ability of powerful and potentially risky therapies to cure SCD.

Trial Name (NCT ID)	Disease	Therapy	Status
Haploidentical Transplantation With Pre-Transplant Immunosuppressive Therapy for Patients With Sickle Cell Disease (NCT03279094)	SCD	Haploidentical SCT	Recruiting
Gene Transfer for Patients With Sickle Cell Disease (NCT02186418)	SCD	Gene Transfer	Recruiting
A Study Evaluating Gene Therapy With BB305 Lentiviral Vector in Sickle Cell Disease (NCT04293185)	SCD	Gene Therapy	Recruiting

Chapter 3:

Evaluating the Accuracy of Patients' QoL Predictions and the Effect of these Predictions on their Clinical Trial Enrolment Decisions

Introduction

Patients who have been recently diagnosed with chronic autoimmune diseases may have an inaccurate understanding of what their QoL is likely to be as their illness progresses while receiving standard clinical care due to the impact bias. This misunderstanding may impact their clinical trial enrolment decisions and may affect their ability to provide a valid informed consent to participate in clinical trials that may increasingly recruit this patient population due to existing treatment paradigms. Little is known about the existence and effect of the impact bias on the QoL predictions of patients who have been recently diagnosed with chronic autoimmune diseases and whether these predictions and patients' expectations of their likely future QoL affect their enrolment decisions. The following chapter outlines a research protocol that addresses these questions. In part 1, we provide an overview of our objectives and hypotheses. In part 2, we outline and justify our methods.

Evaluating the Accuracy of Patient QoL Predictions and their Impact on Clinical Trial Enrolment Decisions: Objectives and Hypotheses

Research Questions

Our research protocol seeks to address two principal questions:

1) Do patients who have been recently diagnosed with chronic autoimmune diseases make accurate predictions of the QoL of patients who were diagnosed with their illness 10 years ago?

2) Do patient QoL predictions correlate with their willingness to enrol in hypothetical risky clinical trials and their predictions of whether a novel treatment will be approved by the U.S. Food and Drug Administration or Health Canada within the next 10 years that would prevent the progression of their illness?

Hypotheses

Based on the available evidence, we have three hypotheses:

1) Patients who have recently been diagnosed with a chronic autoimmune disease will predict that the QoL of a patient who was diagnosed with their illness 10 years ago is lower than the reported QoL experienced by patients who were diagnosed with their illness 10 years ago.

2) Patients who predict that the QoL of a patient who was diagnosed with their illness 10 years ago is poor will be more willing to enrol in a hypothetical risky clinical trial than patients who make more optimistic predictions.

3) Patient willingness to enrol in a hypothetical risky clinical trial will be related to their epistemic prediction of whether a novel effective medication will be approved within the next 10 years that prevents the progression or development of their illness.

Justification

People have been shown to be poor predictors of the QoL of those living with a different health state from their own and to frequently overestimate the emotional and QoL impact of a variety of future events. Patients who have been recently diagnosed with autoimmune diseases are likely susceptible to the same biases and to be overly pessimistic regarding the QoL of a patient who was diagnosed with their illness 10 years ago. Patients who make the most negative predictions may be the most willing to enrol in a hypothetical risky clinical trial in order to gain a potential benefit and stop the progression of their illness. In addition, patients who are the most willing to enrol in a clinical trial may have the strongest belief in the benefits of research trial participation and that a novel treatment that will prevent their illness' progression will be approved within the next 10 years.

Methods

Patient Population and Study Sites

Patients with MS will be recruited at the Montreal Neurological Institute (MNI) and the Jewish General Hospital (JGH), two tertiary research and clinical care centres affiliated with McGill University in Montreal, Canada, at their respective MS and neurology clinics. Patients with MS were selected as our population of interest for two main reasons. First, we wanted to select a setting where impact bias would be most likely to materially affect trial enrolment decisions. Patients with RRMS have many available treatment options. Yet treatments are not curative: patients continue to experience disease progression and symptom worsening. We believe that in this setting, where patients are faced with a difficult enrolment decision, as participation and non-participation each offer potential risks and rewards, the impact bias is most likely to affect enrolment decisions. This contrasts with settings in which patients suffer from diseases with no available treatments, in which enrolment decisions are likely to be heavily swayed by patients' only chance at clinical improvement being available through trial participation and are less likely to be materially affected by impact bias. At the other extreme, the impact bias is also less likely to materially affect patients' enrolment decisions if their disease has extremely effective existing therapies, as they would be unlikely to enrol in a clinical trial testing an aggressive approach irrespective of their affective forecasts. In addition, in these two settings, patient decision-making may be very different from that of patients who have one of the many illnesses that have some available and somewhat effective therapies, which would affect the generalizability of

our study's results to these disease areas. Second, the autoimmune disease chosen to be the disease of interest in our study had to be prevalent in the Canadian population to ensure that recruiting the target sample size would be feasible. MS is common in the Canadian population, as described in chapter 2, fulfilling this criterion.

Patient Recruitment

In order to recruit patients, a member of the clinical or research team will offer patients the opportunity to participate in the study during their scheduled visits to the participating clinics. Patients that meet the inclusion criteria and do not meet the exclusion criteria will be provided with a questionnaire.

The study's inclusion criteria are:

1) Patients must provide informed consent
2) Patients must have been diagnosed with MS between 8 and 12 years prior to their date of trial enrolment OR have been diagnosed with MS within a year prior to their date of trial enrolment
3) Patients must be ≥ 18 years old

The study's exclusion criteria are:

1) Patient does not speak English or French
2) Minors < 18 years old

Patient Consent

The first pages of the study's questionnaires will describe the study and a patient's rights, including their rights to not participate and to stop participating at any time. The questionnaire will also state that continuing to complete the survey signifies their consent to participate. If a patient chooses to complete the questionnaire, once they complete the survey, they will return their completed questionnaire to a member of the clinical or research team.

Study Duration

The study will occur over one year, and data collection will stop once the target sample size of 70 participants (35 patients from each group) is reached. Patient recruitment is currently on hold due to the COVID-19 pandemic. In addition, the study will be terminated if one third of the total expected sample size reports to the clinical or research team that they experienced significant emotional distress due to their participation in the study.

Target Sample Size

Power analysis based on normally distributed responses with a different mean and the same standard deviation suggest that a sample of 70 participants (35 recently diagnosed patients and 35 patients diagnosed approximately 10 years ago) can detect a difference of the same size as previous studies with approximately 80% power.

Questionnaire Design and Data Collection

Patients who have been diagnosed with MS within one year from the date of their enrolment in the trial (recently diagnosed patients) and patients who were diagnosed with MS within 8-12 years from the date of their enrolment in the trial (distantly diagnosed patients) will complete different questionnaires. Questionnaires will be provided in English and French.

1. Measuring QoL predictions:

In order to address our first research question and evaluate the accuracy of recently diagnosed patients' QoL predictions, our questionnaire measures recently diagnosed patients' QoL predictions using three scales. Recently diagnosed patients will predict the overall QoL of patients who were diagnosed with their illness 10 years ago using a visual analogue scale (VAS) and a modified single question version of the time trade-off method and they will predict the domain-specific QoL of distantly diagnosed patients using a Likert scale.

The VAS scale will be oriented vertically and will ask patients to rate what they believe the QoL of a patient who was diagnosed with their illness 10 years ago is on a scale from "the worst QoL that they can imagine" to "the best QoL that they can imagine" by placing a marking in between these two extremes of the scale (see Figure 1). The modified single question version of the time trade-off method will ask participants to mark the number of years X at which they are indifferent in choosing between living with the QoL of a patient who was diagnosed with their illness 10 years ago for 10 years or living with the QoL of a person living in full health for X years. Prior

to completing the modified time trade-off question, patients will answer two sample time trade-off questions to acclimate them to considering a time trade-off. Domain-specific QoL predictions will be captured using a Likert scale by asking patients to report how satisfied they believe a patient who was diagnosed with their illness 10 years ago is in three domains; mobility, social functioning, and occupational functioning (see Figure 2).

We chose to incorporate these three QoL measurement tools into our questionnaire for three principal reasons. First, we wanted to ensure that the scales we utilized provided a robust measure of participants' beliefs while minimizing potential bias. Each QoL measurement tool has strengths and weaknesses and is associated with potential sources of bias. For example, the time trade-off method may be ineffective for evaluating the utility of mild disease states, as respondents are often unwilling to trade any longevity to improve their health status, and the VAS is prone to "end-aversion bias", the tendency of respondents to avoid using a scale's ends [123-125]. Using three scales allows our questionnaire to address each of their limitations and ensures that their biases do not sway our results by allowing us to corroborate our findings across multiple scales. In addition, collecting overall and domain-specific predictions provides a robust measure of patient beliefs. Second, we chose to utilize these scales as our questionnaire needed to be easily understood, short in duration, able to be completed independently by participants, and compatible with clinic work flows to not inconvenience and delay patients and clinicians. A lengthy questionnaire might reduce participation or lead participants to stop completing the questionnaire midway through its completion. In addition, the questionnaire needed to be able to be completed by participants independently without direct guidance from a researcher to

minimize study costs. For these reasons, we chose to use the VAS, a scale widely utilized due to its simplicity, and Likert scales, intuitive categorical scales that are incorporated into numerous QoL assessment tools [123, 125-129]. We considered, but opted against, using existing QoL assessment tools that take participants longer to complete or that require the input of a researcher, such as the traditional time trade-off method, into our questionnaire [130]. However, as we sought to use two different scales to measure participants' global QoL predictions, we chose to utilize a modified version of the time trade-off method that does not require an iterative interview with a member of the research team, as it directly asks participants to state their indifference point (the number of years living in full health they believe are equivalent to living for 10 years in a specific disease state). Directly asking respondents for their indifference point allows the time trade-off method to be used on a paper survey independently in a minimal amount of time, however, some argue that it generates inferior data compared to using iterative personal interviews [130, 131]. Nonetheless, due to the constraints imposed by conducting our study in a clinical setting during patients' scheduled visits, we believe that this modified approach is warranted. Finally, we chose to utilize generic QoL measurement tools and not disease-specific QoL measures, scales that quantify how disease-specific symptoms impact QoL, in order to ensure that our questionnaire could be adapted for use with diverse patient populations and that our results could be directly compared between populations, as differences in patients' predictions would not be due to differences in the scales used [132].

2. Measuring accuracy of QoL predictions:

In order to evaluate the accuracy of recently diagnosed patients' QoL predictions, their predictions will be compared to the current QoL ratings of study participants who were diagnosed with their illness approximately 10 years ago. Distantly diagnosed patients will report their current global QoL ratings using a VAS and a modified version of the time trade-off method, and their domain-specific QoL ratings using Likert scales, similarly to how recently diagnosed patients provided their QoL predictions. The accuracy of recently diagnosed patients' predictions will be evaluated as outlined below in the statistical analysis section.

3. Measuring willingness to enrol in a hypothetical trial and epistemic predictions:

In order to address our second research question and determine whether recently diagnosed patients' QoL predictions are related to their willingness to enrol in a clinical trial employing an aggressive treatment strategy and their beliefs regarding whether a novel treatment for their illness will be approved within the next decade, our questionnaire will measure recently diagnosed patients' willingness to enrol in a hypothetical risky clinical trial and their beliefs regarding the probability that a novel therapy will be approved in the coming years using a Likert scale and a horizontal VAS respectively (see Figures 3 and 4).

4. Additional information collected for analysis:

Our questionnaires will also collect demographic information (participants' age, gender, time since MS diagnosis, MS subtype, and comorbidities) and recently

diagnosed patients' current QoL ratings using a VAS, the modified time trade-off method and Likert scales. This information will allow us to evaluate correlations between these variables and patients' QoL predictions, their willingness to enrol in a trial, and their epistemic predictions.

Data Analysis

After participants' surveys are collected, participant responses will be recorded in Excel. Descriptive statistics will be utilized to evaluate participant demographics including each group's mean age, gender distribution, and MS subtype distribution. Demographic differences between the recently diagnosed and distantly diagnosed participant groups will also be examined. The study's primary and secondary outcomes will be analyzed as outlined below.

The study's primary outcome, the accuracy of recently diagnosed participants' QoL predictions, will be evaluated by comparing the QoL predictions of recently diagnosed participants with the current QoL ratings of patients who were diagnosed with MS 8-12 years prior to their participation in the study for each QoL measurement tool described above. The primary analysis will be made using Student's t-test ($\alpha=0.05$). In addition, we will conduct exploratory analyses testing for the importance of covariates, such as age, gender and comorbidities, using an ANCOVA.

The study's secondary outcomes, identifying the correlations between patient QoL predictions and their willingness to enrol in a hypothetical risky clinical trial and their beliefs regarding the likelihood that a novel effective treatment will be approved

within the next 10 years by the U.S. Food and Drug Administration or Health Canada, will be evaluated using Pearson's R.

Data analysis will be performed using R.

Conclusion

The protocol outlined above will provide the first estimate of the accuracy of the QoL predictions of patients who have been recently diagnosed with a chronic autoimmune disease and the effect of these predictions on their willingness to enrol in a hypothetical risky clinical trial. This information may identify a significant misunderstanding that affects patients' decisions to enrol into clinical trials and a novel lever that investigators may act upon to improve patient understanding and the informed consent process. The following chapter will discuss methodological and conceptual limitations of this project and the potential implications of its results.

Figure 1: Visual Analogue Scale used to Evaluate Participant QoL and QoL Predictions.

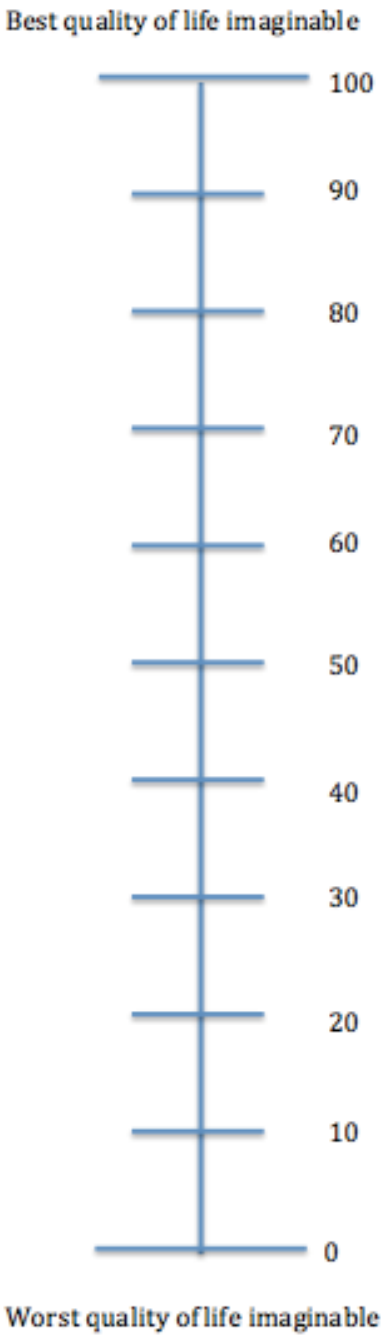


Figure 2: Likert scales used to evaluate recently diagnosed participants' domain-specific QoL predictions.

Indicate below how satisfied you believe **a patient that was diagnosed with multiple sclerosis 10 years ago would currently be** in the following areas of their life:

Ability to get around (for example to walk around):

Extremely Dissatisfied	Dissatisfied	Neither Satisfied or Dissatisfied	Satisfied	Extremely Satisfied

Ability to function socially (for example to interact/visit with friends and family):

Extremely Dissatisfied	Dissatisfied	Neither Satisfied or Dissatisfied	Satisfied	Extremely Satisfied

Ability to work and perform housework:

Extremely Dissatisfied	Dissatisfied	Neither Satisfied or Dissatisfied	Satisfied	Extremely Satisfied

Figure 3: Likert scale used to evaluate the willingness of patients who have been recently diagnosed with multiple sclerosis (MS) to enroll in a hypothetical risky clinical trial.

Researchers want to perform a clinical trial examining whether an aggressive new treatment might completely stop disease progression in patients with multiple sclerosis. In addition to its potential benefit, earlier clinical trials suggest that the treatment could increase risk of infections, increase risk of leukemia, and cause potentially fatal toxicities. In this clinical trial, patients will receive the new treatment, while their disease progression is monitored for two years.

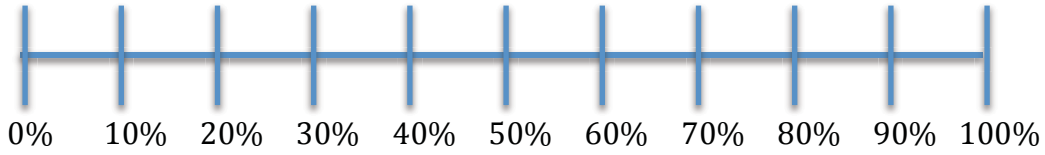
Based only on the information above, please indicate your willingness to enrol in the above hypothetical clinical trial if it were offered to you.

Figure 4: Scale used to evaluate recently diagnosed participants' beliefs regarding whether the U.S Food and Drug Administration or Health Canada will approve a novel treatment within the next 10 years that would prevent the progression of their illness.

Please select on the following scale what probability you believe the following statement has of being true. Where the left of the scale (the 0%) means that you believe there is no chance that this statement is true, while the right of the scale (the 100%) means that you are certain this statement is true.

Statement:

Within the next 10 years, a medication will be approved by the U.S. Food and Drug Administration or Health Canada that will completely stop the progression or prevent the development of multiple sclerosis.



Chapter 4:

Discussion: The Impact Bias' Potential Effect on Clinical Trial Enrolment Decisions: Limitations, Implications, and Future Directions

Introduction

Potential research participants must have an adequate understanding in order to provide a valid informed consent to participate in a clinical trial. This understanding should include having reasonably accurate expectations of their QoL if they decline to participate and their disease progresses while they receive standard clinical care. The ongoing protocol outlined in chapter 3 will provide the first estimate of the accuracy of the QoL predictions for patients recently diagnosed with a chronic autoimmune disease and their relationship with willingness to enrol in a hypothetical risky clinical trial. This project's results may have implications for informed consent and recruitment to clinical trials. Part 1 of this chapter discusses methodological limitations of our protocol. Part 2 discusses conceptual limitations of our project. Part 3 outlines the potential implications of this research and how the informed consent process may be improved to promote patient autonomy. Finally, part 4 discusses future research directions and empirical and conceptual questions that remain to be addressed.

Methodological Limitations of our Protocol

Our protocol has five principal methodological limitations. The first is that our protocol measures recently diagnosed patients' predictions of the future QoL of a hypothetical distantly diagnosed individual, and it infers that these predictions relate to their expectations regarding their own future QoL. We made this design decision after considering the alternatives, which would be to either 1) ask participants to predict their own QoL in 10 years and compare this to the QoL of other patients who have been living with their illness for 10 years or 2) ask individuals to predict their own QoL in 10 years and then, 10 years later, ask these same individuals to rate their QoL. The first option is flawed, as we cannot determine the accuracy of patients' QoL predictions by comparing how their predictions of their future QoL compare to the current ratings of other distantly diagnosed patients. Individuals may account for specific factors in their lives that might affect their future QoL, and it would be wrong to conclude that individuals' QoL predictions are inaccurate because other patients, who may not be impacted by those specific factors, provide different scores of their current QoL. The second option would require 10 years of follow-up, which is not feasible and in any event would be susceptible to loss to follow-up.

The second principal methodological limitation of our protocol is that our questionnaire collects information about participants' willingness to enrol in a hypothetical risky clinical trial, as opposed to collecting information regarding patients' real enrolment choices, and that it collects the QoL ratings and predictions of patients and not real potential trial participants. Our approach assumes that our surveyed patient populations' survey responses are similar to those of potential trial participants and that their reported

willingness to enrol in a real clinical trial reflects what their real enrolment choices would be if they were offered the opportunity to enrol in a clinical trial. The surveyed patient population may not accurately reflect the population of patients who are offered the opportunity to participate in trials and patients' reported willingness to enrol in a trial may be different from their real enrolment choices, which would impact our study's findings.

The third methodological limitation of our protocol relates to the manner in which patients are recruited to participate. Recruiting participants during their clinical visits with their neurologist may introduce biases that impact our study's results. Distantly diagnosed patients who present most often to clinic may have more severe and refractory disease than the average MS patient or have more significant comorbidities that complicate their treatment and necessitate frequent follow-up. This would lead severe complex cases of MS to be overrepresented in our sample. These patients may report a substantially lower QoL than the average patient living with MS in the community would report, which would affect our primary outcome. Recently diagnosed patients may provide an accurate assessment of the true average QoL of a distantly diagnosed MS patient in the community while our sample of distantly diagnosed patients, in which severe cases may be overrepresented, may provide a substantially lower QoL. This would lead us to falsely conclude that recently diagnosed patients have inaccurate QoL expectations. Similarly, patients may present to clinic for routine follow-up or due to an acute exacerbation of their illness. Distantly diagnosed patients suffering from an acute exacerbation may report a lower current QoL than the average QoL of a distantly diagnosed patient living in the community, which would affect the accuracy of our conclusions. In addition, recently diagnosed MS patients who present most frequently to clinic may also have severe frequently relapsing forms of MS

and early severe disability, which may impact their willingness to enrol in a potentially risky clinical trial.

The fourth methodological limitation concerns our study sites. The Montreal Neurological Institute and the Jewish General Hospital are tertiary academic centers whose patients may not reflect the average MS patient. Patients recruited at these hospitals may have been referred as they are experiencing rapidly progressing or refractory disease in order for them to benefit from the care of neurologists with extensive experience managing such cases. If the patient population at these clinics does not reflect the average MS patient, then their reported QoL may be significantly different from that of the average MS patient, which would impact our results.

The final methodological limitation that we will discuss involves the known difficulty in interpreting patient reported expectations [133]. Individual patients derive their beliefs from different sources, they may interpret questions differently from what was intended, and they may report their expectations with an individual goal in mind, which may affect our conclusions [133]. For example, in our study, patients may believe that thinking positively about their future QoL (having hope) will benefit them emotionally and be unwilling to express their true expectations that affect their enrolment decisions. In addition, patients may have different understandings of our scales and questions, such as having different beliefs regarding the best and worst QoL that they can imagine, which would impact their reported expectations. We designed our protocol to limit the challenges associated with interpreting patient expectations, however, these challenges must be considered when interpreting our study's results.

Future studies may be developed to address these five limitations and to verify our study's conclusions. In addition to these methodological limitations, our project has several conceptual limitations that must be considered prior to utilizing our study's results to alter existing recruitment strategies and informed consent requirements, which we will now discuss.

Conceptual Limitations of our Project

Our project has three conceptual limitations as well. The first is that our project is premised on the argument that accurate knowledge of one's likely future QoL if one were to receive standard care and not participate in a clinical trial, is required to provide a valid informed consent. Critics such as bioethicist Nada Gligorov may argue that the impact bias does not diminish patient autonomy and that understanding one's future QoL is not required to provide a valid informed consent [134]. Gligorov argues that affective forecasting errors do not impair "a person's ability to understand the diagnosis, prognosis, and likelihood of risks and benefits and treatment alternatives" nor their ability to apply this information to their own specific circumstances [134]. She argues that as the impact bias does not impact these abilities, it does not impair the understanding that patients need to provide an autonomous consent [134]. Although it is true that affective forecasting errors do not impair a patient's ability to understand the probability of their illness progressing and symptoms worsening, they do affect how patients appreciate this information. Gligorov's argument is based on the assumption that patients must only understand "medical information about treatment alternatives" to have the capacity to

make a treatment decision [134]. This reflects a narrow definition of what represents sufficient understanding that contradicts most accounts of the purpose of informed consent: "to protect and enable meaningful choice" [135]. Although understanding one's diagnosis, prognosis, and the benefits and risks of all available treatments is required to have sufficient understanding to make a rational decision, as we have seen in chapter 1, simply understanding the likelihood of specific medical events may not be adequate to enable rational treatment and enrolment decisions that allow patients to achieve their goals, and providing those patients who seek to make rational decisions with the information that is required to make such decisions should be the aim of the informed consent process. If optimizing QoL is a factor that patients aim to achieve, they must not only understand their diagnosis, prognosis, and the probabilities that specific treatment effects will occur (epistemic forecasts), but also how their lives, their emotional state, and their QoL will be impacted by these events (affective forecasts). Patients who harbour a significant misunderstanding regarding their future QoL should be considered to potentially be unable to provide a valid informed consent to participate in a clinical trial. Attempts should be made to correct this misunderstanding in either specific patients who are identified as harbouring inaccurate QoL expectations or in all patients who are offered the opportunity to enrol in clinical trials, as will be discussed below.

The second conceptual limitation of our project is that it may be argued that claiming that a patient's consent to participate in a clinical trial is not valid due to poor affective forecasts and subsequently preventing their participation is paternalistic and diminishes patient autonomy as opposed to promoting it. Systematically preventing patients with inaccurate expectations of their future QoL, based on their physician's

assessment, from participating in clinical trials may indeed diminish patient autonomy. In addition, on an individual patient level, it is inaccurate for a physician to state that a patient's expectations regarding their own future QoL are wrong, simply because they are different from the average QoL experienced by patients who have been living with their illness for years. Nonetheless, as will be discussed below, we do not argue that our study's results should be used to justify preventing patient enrolment in clinical trials during which they may receive otherwise inaccessible interventions that may improve their health outcomes. Instead we believe that they may be used to justify developing educational interventions to limit the effect of the impact bias in order to improve patient understanding and to allow patients to make more rational decisions that better allow them to optimize their well-being and achieve their goals. These interventions may be argued to be paternalistic, however, as Rhodes and Strain outline, "some degree of paternalism may … be justified to prevent people from making decisions based on distorted estimates of their future responses" [26]. The interventions we propose would not reduce patient agency and autonomy by restricting their access to trials and preventing them from acting on their desires, but would instead promote them by allowing patients to better pursue their interests.

A third conceptual limitation of our project is that many of our arguments are based on the assumption that patients are rational decision-makers who make decisions to optimize positive outcomes, such as their QoL. We argue that if the impact bias' effect on patients' QoL expectations were reduced, patients would have more accurate QoL expectations and be better able to make rational enrolment decisions. Many would likely argue, and we would agree, that patients are not solely rational decision-makers who seek

to maximize utility, and that their decisions are not necessarily rational. Patients may choose and have a right to make decisions that are not based on rational grounds. They may continue to argue that forecasting biases that impair their ability to make a completely rational decision are therefore not concerning as they already do not make perfectly rational decisions. However, one of the main purposes of the informed consent process is to ensure that patients that aim to make rational decisions have the necessary information to allow them to do so. Patients must be informed of the risks and benefits of trial participation and of their respective chances of occurring, as this knowledge allows them to make a more rational decision than they could have if they did not have this information, which ensures their epistemic forecasts are reasonably accurate. Affective forecasting errors may impair a patient's ability to make a rational decision similarly to errors in epistemic prediction, as they may lead patients to harbour a misunderstanding regarding a factor that is essential to their ability to make a rational decision to enrol in a clinical trial, their likely future QoL. For this reason, investigators should similarly aim to ensure that patients' QoL expectations are reasonably accurate to help promote the ability of patients, who may aim to make rational decisions, to make rational decisions that allow them to achieve their unique goals.

Potential Implications of our Research: Improving Patient Understanding and the Informed Consent Process

Despite the above limitations, if patients are found to make inaccurate overly pessimistic predictions regarding the QoL of patients who were diagnosed with their

illness 10 years ago and patients' QoL predictions are found to correlate with their willingness to enrol in clinical trials testing aggressive treatment approaches, then members of the research enterprise should be concerned about consent validity. If this is the case, investigators should attempt to address this barrier to informed decision-making by enhancing the accuracy of patients' QoL expectations to ensure that patients do not enrol in clinical trials based on a misunderstanding, which as outlined in chapter 1 would be ethically concerning for four principal reasons. First, if members of the research enterprise intentionally avoid resolving this potential misunderstanding during trial recruitment, one could argue that the research they carry out or supervise exploits participants' misunderstandings to advance individual or institutional interests. Second, these patients may be putting themselves at risk of experiencing significant harms on the basis of a misunderstanding. Third, not attempting to improve patient understanding to improve participants' abilities to make fully autonomous rational decisions disrespects participant dignity, and finally, intentionally not addressing this misunderstanding may diminish the public's perception of the scientific enterprise and lead to significant societal harm. Requiring patients to have the opportunity to participate in interventions that aim to enhance the accuracy of their QoL expectations would address these ethical concerns by reducing this potential source of patient misunderstanding.

Little is known about how the impact bias may be reduced to improve patients' affective forecasts and to improve the accuracy of their QoL expectations. We will now outline interventions that address individual contributors to the impact bias and that aim to holistically improve the accuracy of patients' expectations and describe how they may be incorporated into standard recruitment procedures.

Improving Patient QoL Expectations

Defocusing exercises, interventions that ensure that patients consider diverse aspects of their future daily life and not only those that will be impaired by their illness' progression when they evaluate how their QoL will change as their illness progresses, may be developed and incorporated into practice to address focalism. These interventions may be based on previously evaluated defocusing exercises, such as that of Wilson et al., who determined that focusing subjects on their daily activities through the use of a "diary questionnaire" may improve subjects' affective forecasts outside of the medical context [20, 21]. For example, a questionnaire similar to Wilson et al.'s that asks patients to report the number of hours they will spend on a variety of activities in one day may defocus patients and improve the accuracy of their QoL expectations [20]. Other interventions to address focalism may include discussions with a member of the research team or an independent professional chosen by an institution's research review board, during which patients would be encouraged to discuss the enjoyable aspects of their life that might be unaffected by the progression of their illness. These interventions may involve one-on-one interactions or take place in a group setting and may incorporate multimedia components, which have been shown to increase patient understanding during the informed consent process [136].

Other interventions may target immune neglect, an individual's failure to identify that their protective psychological "immune system" will allow them to overcome their initial negative emotional reactions to the progression of their illness [10]. These may include one-on-one or group-based interventions during which patients discuss how they overcame significant emotional distress in the past in order to remind them of their ability to cope with and overcome negative emotional reactions to stressful events, or during

which they may discuss how family members and friends overcame emotional distress [10]. In addition, cognitive behavioural therapy has been suggested as a method that may be used to address immune neglect to improve patient understanding [10].

Researchers may also develop and implement interventions that improve patients' abilities to predict how they may adapt to their changing health status. These interventions may include discussions with patients centered on how they adapted to past changes in their lives that at first seemed overwhelming or on how their family members or acquaintances adapted to health challenges, such as losing their mobility, perhaps by developing new interests, such as reading and writing. In addition, investigators may use multimedia-based interventions using the narratives of other patients who have adapted to the progression of their illness and developed new hobbies from which they derive joy [10].

Finally, in addition to interventions that solely target specific contributors to the impact bias, researchers may develop holistic interventions to improve the accuracy of patients' QoL expectations. For example, patients may be provided with opportunities to meet or contact other patients and clinical trial participants with their condition in-person, via telephone, or in an online forum. These peer-education initiatives may focus on the individual contributors to the impact bias, such as discussing how distantly diagnosed patients adapted to the progression of their illness, or they may be unstructured. These opportunities may be valuable to recently diagnosed patients, who have limited experience living with a progressive chronic condition, by providing them with the opportunity to learn from others who have had experience overcoming challenges related to their illness'

progression. Evidence suggests that these initiatives may lead patients to be more optimistic regarding their future QoL [10].

Implementing Interventions in Practice

Prior to implementing these interventions into standard recruitment procedures, research must be performed to evaluate whether the impact bias affects clinical trial enrolment decisions and impairs rational decision-making, such as the study outlined in chapter 3, and to determine if interventions that aim to address the impact bias have a positive impact on patient understanding and whether this translates into improved patient satisfaction with their enrolment decisions. Once this research is conducted, effective interventions that promote rational decision-making should be implemented in a manner that is not paternalistic and that does not overburden investigators and prevent the conduct of valuable research. This is essential as overly paternalistic approaches will diminish patient autonomy and may impair the physician-patient relationship, as patients may resent physicians who prevent their trial participation. Overly time-consuming or resource-intensive interventions would not be feasible to implement into practice and might impair trial recruitment. In addition, identifying individual patients who harbour inaccurate expectations of their future QoL may be difficult for investigators, which may limit the efficacy of interventions that rely on effectively identifying individual patients who harbour inaccurate expectations.

In order to address these concerns we propose that:

1) Investigators and research review boards consider implementing interventions, once they are shown to be effective, to improve patient QoL expectations into a trial's recruitment process under the circumstances outlined in chapter 2, in which affective forecasting errors are particularly concerning.

2) Individuals involved in trial recruitment assess patients' QoL expectations during the recruitment process and consider referring patients with a poor understanding of their likely future QoL to their treating physician and recommend they participate in an intervention to improve the accuracy of their expectations.

3) All patients be offered the opportunity to participate in interventions to improve the accuracy of their QoL expectations during trial recruitment. This may involve mentioning the intervention during recruitment discussions and ensuring a trial's consent form and recruitment documentation/handouts outline the intervention and its purpose.

These three suggestions will ensure that 1) trials in which affective forecasting errors are the most concerning will incorporate interventions to reduce their impact on patient decision-making, 2) patients with QoL expectations that are likely to be inaccurate will have the opportunity to discuss these expectations with their treating physician and to benefit from their counsel and interventions to address their beliefs, and 3) all patients will

have the opportunity to benefit from improving the accuracy of their QoL expectations in order to make more rational decisions that reflect their values and allow them to achieve their goals. We do not recommend that patients should be prevented from participating in a trial based on a study investigator's assessment that their QoL expectations are likely to be inaccurate. We instead recommend that these patients be referred to their treating physician to discuss their expectations and that they participate in an educational intervention prior to enrolling in a trial, if they desire.

Future Directions

Our project will provide the first estimate of the effect of the impact bias on research participants' clinical trial enrolment decisions. Future conceptual and empirical projects will need to be conducted to further elucidate the effect of affective forecasting errors on informed consent and the resulting ethical implications. We will now describe three important questions that future research might address.

We have discussed that on an individual patient level we cannot be certain that a particular patient's expectations are wrong simply because they differ from the average QoL experienced by distantly diagnosed patients. This has led us to not recommend preventing individual patients from enrolling in trials due to their physician believing their expectations are inaccurate. However, one might argue that patients who harbour extremely inaccurate QoL expectations should not be eligible to participate in a trial. Further work will need to be conducted on how investigators can address this issue in a manner that is not overly paternalistic. Scales may need to be developed that measure

patient QoL expectations to identify patients with extremely inaccurate expectations in a systematic fashion and the research community will need to clearly delineate how inaccurate QoL expectations must be in order to render an informed consent invalid. These scales may utilize existing disease-specific or generic QoL measures and their validation will require a large dataset of distantly diagnosed patients' QoL ratings. This research should include diverse stakeholders, including patients and patient advocates, in its development, conduct, and interpretation in order to ensure it serves patient interests and promotes their autonomy without overly restricting their ability to act on their desires.

In addition, we have discussed the impact bias' potential negative effect on patient understanding and autonomy, but have not yet considered that the impact bias may have a positive effect on patient satisfaction and well-being. Impact bias might serve an important function in people's decision-making processes, despite its negative effect on patient understanding in the context of clinical trial enrolment. For example, the impact bias may lead patients to be more willing to embrace medical actions that may enhance their well-being compared to if their decision was not influenced by the impact bias and they chose to not participate. For example, patients with MS who harbour inaccurate QoL expectations due to the impact bias may be more likely to enter clinical trials and may experience improved satisfaction with their enrolment decision and overall well-being compared to patients who participate in interventions that limit the effect of the impact bias. This aligns with Blumenthal-Barby and Ubel's argument that unrealistic beliefs may lead patients to make beneficial decisions [137]. Future studies might evaluate whether patients who participate in interventions that improve the accuracy of their QoL expectations report higher or lower satisfaction with their enrolment decisions and overall well-being. If the

impact bias is adaptive and extirpating it reduces patient QoL, for example by leading patients to experience more regret and dissatisfaction with their clinical trial enrolment decisions, then despite its potential ability to impair understanding, some may argue that it should not be targeted by educational interventions.

In addition, the impact bias may interact with other factors that are believed to impair patient understanding, such as therapeutic misestimation and therapeutic misconception, two factors that may affect patients' epistemic predictions. Different contributors to patient misunderstanding may be cumulative in nature, leading misunderstandings that on their own would not render a decision substantively non-autonomous to combine to significantly impair understanding and rational decision-making. In addition, individual contributors to patient misunderstanding may increase the magnitude of others or increase an individual's likelihood of experiencing others. For example, patients exhibiting therapeutic misconception may make less accurate (more biased) affective forecasts or be more likely to make inaccurate affective forecasts. Future research may delineate the relationship between different contributors to patient misunderstanding in order to identify patients that are most susceptible to making enrolment decisions based on misunderstandings and to develop interventions that simultaneously correct multiple misunderstandings in order to optimally promote patient autonomy.

Finally, we have solely focused on the impact bias' ability to affect patients' and their decision makers' choices. The impact bias may also affect physicians' beliefs and choices in a manner that affects their practice and that impacts patient care, as outlined by Rhodes and Strain [26]. For example, physicians may believe that a treatment's side effects would

be unbearable for a patient and lead to a substantial reduction in their future QoL without considering that their own beliefs may be affected by the impact bias [26]. This may lead them to not offer this treatment to their patient. If physicians were made aware of how their beliefs may be affected by the impact bias, they may make more accurate forecasts of their patients' QoL and offer such treatments to their patients, enhancing their autonomy and agency. Future research may elucidate how the impact bias affects physicians' beliefs and decision-making and impacts patient outcomes, which may identify the need to implement interventions that educate physicians regarding how the impact bias may affect their beliefs and management decisions into continuing education programs and medical student and resident education.

Conclusion

In conclusion, the impact bias may affect patients' understanding and impair their ability to make fully rational enrolment decisions. Future studies should build upon our protocol's results, address its limitations, and determine whether practical interventions can improve the accuracy of patients' QoL expectations in order to improve their ability to make rational decisions that allow them to achieve their unique goals. These interventions may target specific contributors to the impact bias or be holistic in nature. They should be designed to be practical to implement into the standard recruitment procedures of trials in which affective forecasting errors are most concerning in a manner that promotes patient autonomy, agency, and satisfaction with their enrolment decisions.

Conclusion

As we have seen, people have been found to be poor predictors of their emotional responses to future events, the QoL of others living in different health states, and their own future QoL due to the impact bias. We have outlined how these predictions may affect patients' expectations and clinical trial enrolment decisions and how inaccurate emotional forecasts and QoL expectations may affect consent validity. In addition, we have identified conditions in which the impact bias is most concerning and developed a protocol that will identify whether patients' enrolment decisions are materially affected by the impact bias. Researchers should be concerned regarding the impact bias' potential ability to impair patient autonomy and should consider implementing interventions, which may be developed, to promote the ability of patients to make better informed rational decisions that allow them to achieve their goals.

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