# Understanding treatment decisions from the perspective of People with Relapsing Remitting Multiple Sclerosis: A critical interpretive synthesis

Eskyte, I., Manzano, A., Pepper, G., Pavitt, S., Ford, H.L., Bekker, H.L., Chataway, J., Schmierer, K., Meads, D., Webb, E., Potrata, B.

**Abstract**

*Background* Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disorder of the central nervous system that mainly affects young adults. While there is no cure for MS, disease modifying treatments (DMTs) reduce relapse rate and partial accrual of disability. More effective DMTs may have higher risks including life-threatening infections or secondary autoimmunity. The complexity and novelty of available treatments cause challenges for clinicians when prescribing treatments and for people with MS (PwMS) when deciding what trade-offs they are willing and ready to make.

*Objective* To explore the experience of people with relapsing remitting MS (PwRRMS) and their perspectives in choosing treatments.

*Methods* Critical interpretive synthesis was employed to review and synthesise the published literature. Eighty-three publications were selected in a multi-step systematic process.

*Results* Findings are presented in four interrelated areas: the influence of the clinical evidence-base in decision making; the meaning of DMT efficacy for PwRRMS; the influence of models of decision-making and information acquisition practices in PwRRMS; and the importance of psychosocial dimensions in DMT decision making. Synthesis of the findings revealed that alongside medical and individual reasoning, contextual circumstances play an important role in making treatment decisions.

*Conclusion:* This review identifies and explains the importance of diverse contextual circumstances (clinical, social, psychological) that are important for PwRRMS when making treatment decisions. The findings demonstrate the importance of eliciting, understanding and addressing such contextual factors.

**Keywords**: Multiple sclerosis; relapsing-remitting multiple sclerosis; disease-modifying treatments; decision-making; person-focused care; decision-support techniques.

## 1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disorder of the central nervous system [1, 2]. Around 85% of all people with MS are diagnosed with relapsing remitting MS RRMS [3, 4] which is usually characterised by episodes of neurological dysfunction followed by remission that often causes increased levels of residual impairments [1, 5, 6] but some people may not fully recover after a relapse. The last decade has seen a rapid increase in the number of licensed disease modifying treatments (DMTs) for people with RRMS (PwRRMS). Evidence suggests that in many PwRRMS early treatment with highly active DMTs (i.e. alemtuzumab, natalizumab, fingolimod) can reduce relapse frequency and disability accrual [7-12]. However, many of these DMTs have a high risk of adverse health outcomes, including life-threatening infections or secondary autoimmunity. This complex array of treatment options creates difficulties for physicians in recommending DMTs, and for PwRRMS who have to trade-off possible negative consequences with long-term benefits.

In the context of MS, where PwRRMS have uncertain disease trajectories, understanding of information is important for making informed treatment decisions [13, 14] and ensuring that people gain control and anxiety is reduced. Patients' treatment preferences and information needs, however, are heterogeneous, changeable over time and, most importantly, context-dependent [15]. Although several preference surveys have been conducted, qualitative research within them is limited [16]. Specifically, it is not yet understood *when* PwRRMS prefer to start treatment after diagnosis, *why*, *which type of DMT* and *how* their choices are related to treatment attributes (risks, benefits, side effects, mode of administration, etc.). Given the lack of theoretical development to explain what underlies the treatment preference of PwRRMS, this article reports findings of a systematic review using a critical interpretive approach to fill these conceptual gaps. It offers a theoretical framework identifying from the perspective of PwRRMS important clinical, social and psychological contexts associated with their treatment decision making. This synthesis was undertaken to inform a two-year MS Society funded project (CRIMSON – Considering the Risks and Benefits in Multiple Sclerosis Treatment Decisions) (2016–2018) whose aim is to improve understanding of how PwRRMS weigh up the pros and cons of treatments. It was one activity undertaken to inform a discrete choice experiment to investigate these trade offs.

## 2. Methods

A systematic review using Critical Interpretative Synthesis method [17] was used to synthesise a large, and/or methodologically and thematically heterogeneous

literature [18-20] to investigate how various dimensions impacting shared decision making are important when PwRRMS make DMT decisions. The analysis aims to generate theoretical categories (hypotheses) based on the critical interpretation of the assumptions within the literature. These can then be tested (discarded/refined) in further investigations. In our review, these hypotheses are expressed as a general conceptual framework to explain the contextual circumstances in which PwRRMS decide what is important about treatments. Peer reviewed qualitative, quantitative and mixed-method studies, grey literature, systematic reviews, non-empirical studies and policy documents were eligible for inclusion to capture PwRRMS perceptions and experiences of treatment decisions. At the time of the review there were 12 DMTs approved and licensed for PwRRMS in the UK.

Inclusion criteria:

- Peer-reviewed articles published between 1993 and 2017 were included if they examined how PwMS consider risks and benefits of the spectrum of DMTs.
- Research and policy reports available on health and social science databases.
- Studies written in English.

Exclusion criteria:

- Studies about children under age of 16.
- Studies dealing with Eastern and alternative (exclusively) medicine.

## 2.1. Data extraction, synthesis strategy and quality assessment

The electronic literature databases searched were: Medline, Sociological abstracts, PsycInfo, CINAHL, Social work abstracts, Ovid, ASSIA, Web of Science, EBSCO host and Google Scholar. Search terms were identified following consultation with clinicians, researchers and PwMS; they were aimed at identifying studies on the experiences of PwRRMS of starting and taking DMTs and how different social and health factors influence experiences when starting and taking DMTs. These were as follows: Relapsing Remitting Multiple Sclerosis, disease modifying treatment, risk*, choos*, tak*, side effect*, prefer*, fatigue, uncertain*, deci*, treatment experience, percept*. Further search terms relating to how clinicians communicate potential risks, benefits and uncertainty of DMTs and how this communication shape PwRRMS' perceptions of risks and benefits were: Relapsing Remitting Multiple Sclerosis, disease modifying treatment, risk*, side effect*, prefer*, fatigue, uncertain*, decision mak*, communicat*, pregnan*, parent*.

The established [17] literature search, selection, coding and quality assessment protocol was followed. Quality, relevance and rigour of studies were assessed by the synthesis team (IE, AM) considering the methodological value of findings in the context of each study's aims and how they helped developing initial hypotheses to answer our review questions. A data extraction sheet stating the methodological approach against the aims of the studies was created as a tool to assess inclusion criteria. In the case of disagreement, the two researchers reviewed the papers again and discussed to achieve consensus. Relevant full text papers were mapped into 16 initial emerging theoretical categories (see Table 1). Within these categories, studies were examined by IE and AM in more detail (8 areas each) and the results compared. The search of bibliographic databases to cover more sources on parenthood was updated as this emerged as a key factor affecting DMT decisions for some PwRRMS. In the second stage of the review, initial constructs were identified and contrasted across sources. The synthesis team met face-to-face and refined or discarded emerging constructs with the CRIMSON study (Considering Risk and benefits In Multiple Sclerosis treatment selection) Patient Public Involvement (PPI) representative and lead (GP, SP) and with the wider project team (rest of authors).

**Table 1. Initial theoretical categories**

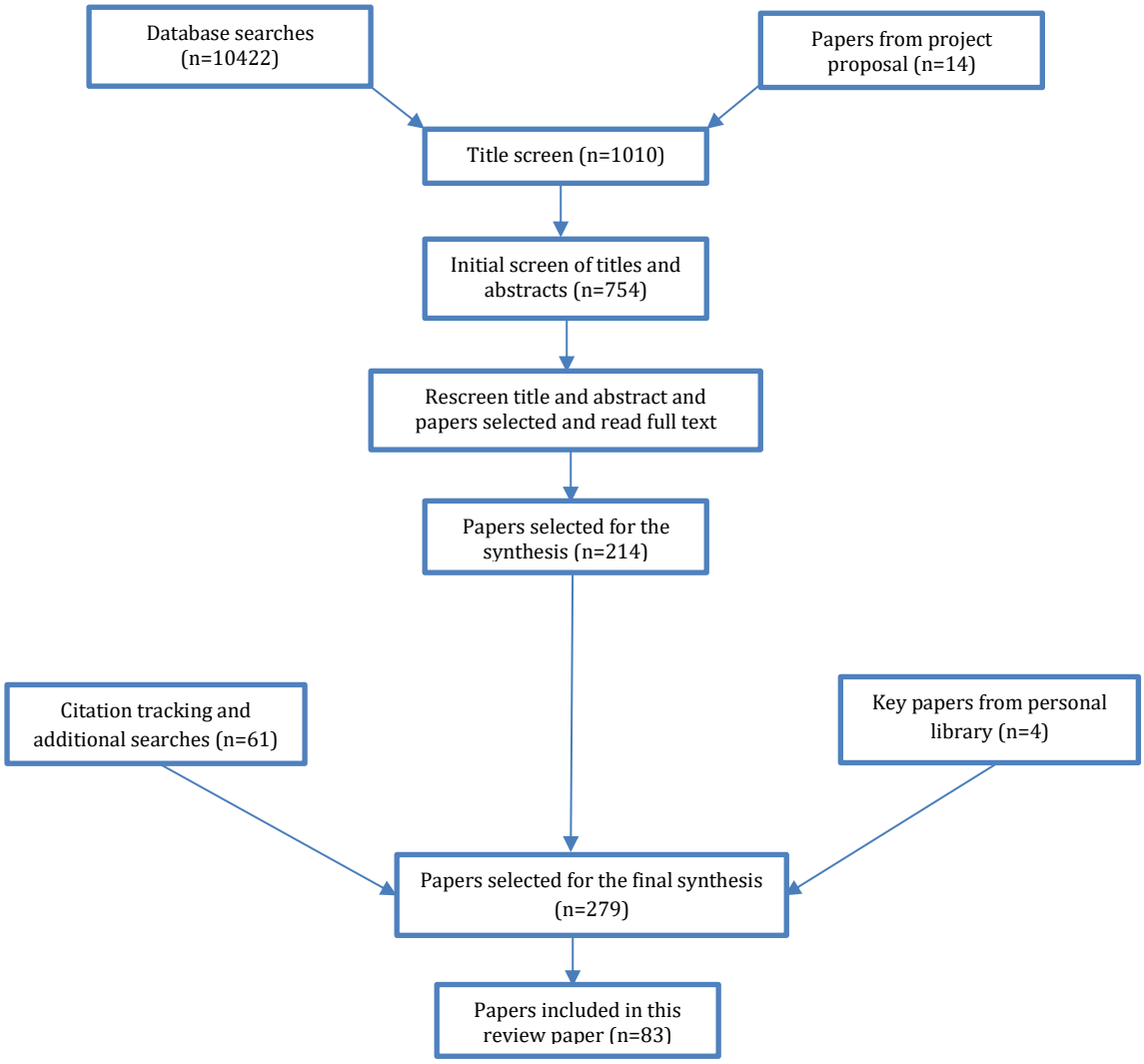
| | **Themes** |
|---|---|
| 1. | Coping strategies: MS and DMTs |
| 2. | Decision making practices and processes |
| 3. | How the impact of MS on one's dignity shapes treatment decisions |
| 4. | Employment and treatment decision |
| 5. | How experience of fatigue shapes treatment decision |
| 6. | How gender differences influence decision making |
| 7. | Hope to 'get better': decision when and which treatment to choose |
| 8. | Injections: fear and inconvenience |
| 9. | Interaction with health care professionals |
| 10. | How parenthood-related positions and practices influence treatment decision making |
| 11. | Patient experience: managing positive and negative aspects of treatment |
| 12. | Perceptions and experiences of quality of life before and after starting treatment |

| | |
|---|---|
| 13. | How treatments impact one's sexuality |
| 14. | Side effects: experience and management |
| 15. | Treatment decision: practice and process |
| 16. | Uncertainty about treatment effectiveness and side effects in managing the illness |

## 2. Results

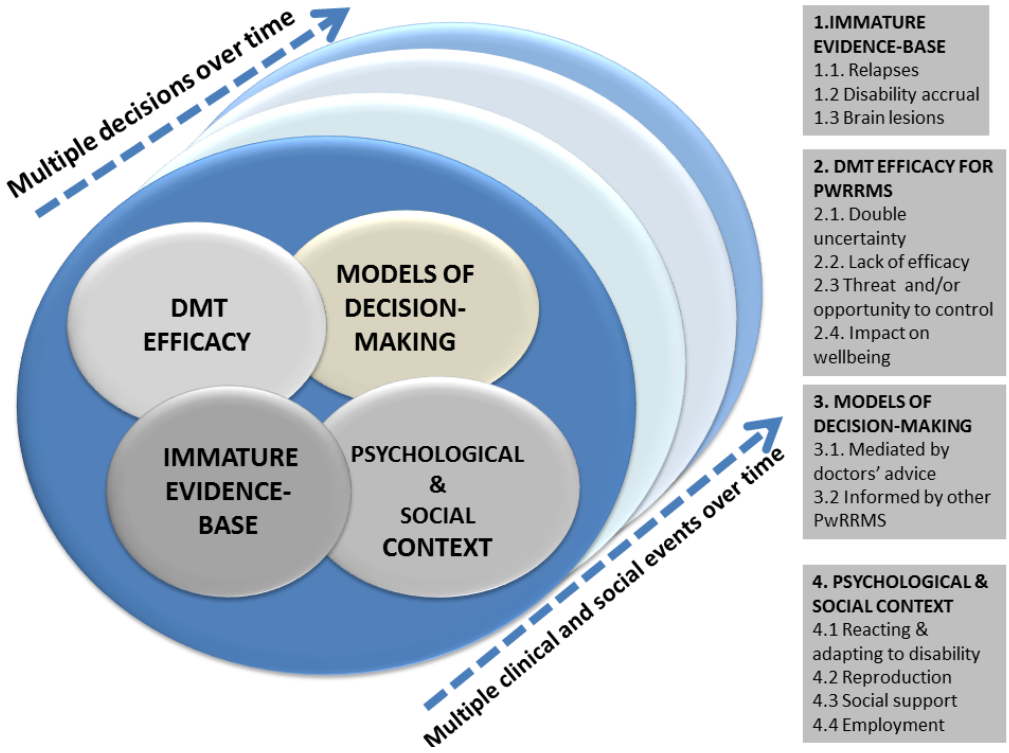
The search terms identified 279 studies; 83 fulfilled the inclusion/exclusion criteria (see Figure 1). Studies excluded at the last stage were those without explicit PwMS input and papers offering useful conceptual insights were prioritised. A diverse multidisciplinary literature was reviewed (medicine, nursing, applied healthcare, psychology education, communication studies, sociology of health and illness and disability studies).

**Figure 1. Synthesis process of the selected literature**



The review highlights the complex clinical, psychological and social dynamics underlying DMT decision-making. The final framework (See Figure 2) included 4 domains: the immature evidence-base about the condition, the meaning of DMT efficacy for PwRRMS, the models of decision-making in MS, and the psychological and social context in PwRRMS. There are interactions between all these domains at different decision points which take place over time after multiple clinical and social key events. This dynamic nature of decisions was incorporated in the diagram format [21].

**Figure 2. A person-focused framework for understanding DMT decisions in RRMS**




## 2.1. The influence of the clinical evidence-base in PwRRMS treatment preferences

The patient journey to a definitive diagnosis of MS and treatment initiation varies in duration; it is not uncommon for diagnostic uncertainty with an abundance of tests being undertaken. Definitive diagnosis is typically dependent on achieving a referral to a specialist neurologist who then triggers key neurological history, examination and pertinent investigations and onward treatment management. Diagnostic criteria have been in constant revision during the last 20 years and are based on the observation of central nervous lesions disseminated in time and space, through clinical history of relapses and clinical examination. Whilst DMT guidelines are

evolving [22], an evidence-based approach to patient-centred clinical decision making in MS is lacking. Treatment management has been focused towards three essentially "contested" measures that are aggregated to assess DMT effectiveness and disease progression:

1. Relapses in PwRRMS are highly variable within a person and across patients. They are unpredictable (when and how) and may involve a variety of physical, motor, sensory and cognitive symptoms [23]. Although there are accepted general principles determining what a relapse is, definitions vary, which has significant implications for diagnosis, prognosis and relapse management [24]. The literature review has revealed that PwRRMS' relapse experiences are legitimised by clinicians assessing duration and associated symptoms but challenged by the difficulty of standardising, measuring and timing relapse characteristics. Disagreements between PwRRMS and physicians about relapses are common [25] and each relapse, clinically relevant or not, has associated functional, psychological and social challenges [26]. This uncertainty has a direct impact on PwRRMS' treatment preferences. Specifically, relapses that do not significantly intrude into everyday life and are tolerable often encourage PwRRMS to either consider starting less effective DMTs or not to start at all. On the other hand, if relapses significantly affect a patient's life and challenge future plans, this often lead to a decision to start more effective and riskier DMTs.

2. Disability accrual is measured with a number of general and MS-specific instruments which are also used in DMT trials. They measure physical functioning and monitor the speed in which MS is progressing (how fast/slow impairments appear and stay). The choice of instruments seems to be affected by format; feasibility; interpretability of the scoring mechanisms and of clinically meaningful values; acceptance by PwMS; and international recognition as a primary outcome in trials. From a person-centred focus, frequently used disability accrual instruments such as the Expanded Disability Status Scale (EDSS) [27] have many clinical [28, 29] and theoretical [30, 31] shortcomings. It is difficult to estimate the typical speed of any deteriorating disease from intermittent clinical observations, which is inherently uncertain, because the exact times of events of interest are self-reported and not always known, and they often lie in the intervals between scheduled clinic visits [32]. The longer the interval is between observations (clinic visits for EDSS assessment), the larger is the interval censoring bias and underestimation. In MS disability progression speed from clinical observations vary greatly, and on average disability accrues slowly and severe disability develops in many RRMS patients within twenty years of onset [33].

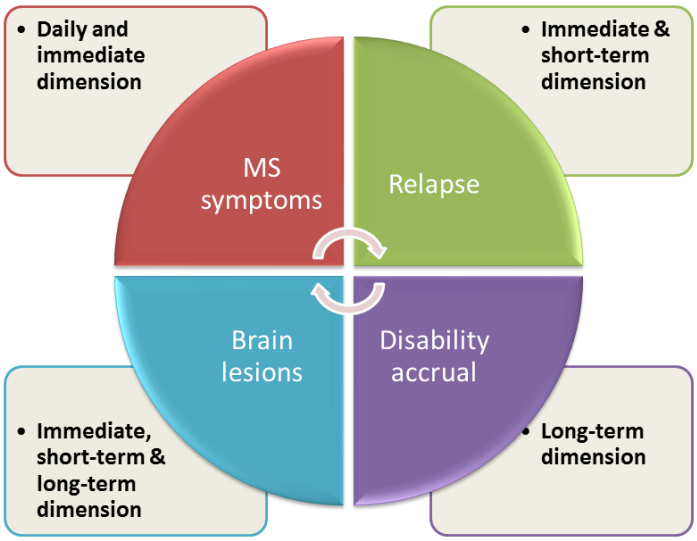
3. Brain lesions. Over the past 25 years, MRI has become a key tool to underpin a diagnosis of MS. It is also valuable in treatment monitoring though there are occasional cases with very few (or indeed no) lesions detectable on MRI, and yet the

diagnosis is MS. The review suggested that although MRI is used in diagnosis and recommended to monitor progression and DMT efficacy, not all centres and clinicians routinely use them to monitor response to therapy due to cost and access. If MRI is not implemented routinely then only one (relapse) of the two key measures (relapse + MRI lesions) is used as a proxy for a less aggressive course.

MRI should not be treated as the only or the main instrument for diagnosing and monitoring MS [34]. Nevertheless, it is a preferred tool for clinicians and PwRRMS to visually trace illness progression [35]. PwRRMS value the information produced by MRI scans [36] and MRI information guides them when considering potential treatment options, i.e. when to start/delay/switch DMTs [36-38]. MRIs can be emotionally challenging for PwRRMS as they can indicate and advancement of the disease, even when patients are not experiencing an increase in symptoms [23]. Alternatively, they may not illustrate a change in lesions when symptom burden is increased. In such a context MRI scans either legitimise or disavow patients' experienced symptoms and relapses [39]. This suggests that there is not always a correlation/relationship between relapses as defined by MRI scans/clinical tests and relapses as defined by people's experiences of symptom worsening. This has important implications because clinicians are the gatekeepers to the treatments and they rely more on MRI scans and clinical tests, whereas PwMS, who have to make the decision, rely more on the lived experience of MS and their own experiences of relapses. This suggests a potential mismatch in the clinical evidence and patient experience symptoms being used when making treatment decisions, and consequential challenges in choosing treatments.

Our review revealed a 'temporal disconnection' of these three main MS measures (See Figure 3). While MS symptoms affect daily lives, relapses relate to an immediate or short-term timeframe, disability accrual relates to future long-term health outcomes and the MRI is a temporal representation of those simultaneously: present, future and past. This temporality conundrum plays an important role in PwRRMS' understanding of DMTs because although they are an investment for the future (improving long-term health outcomes), they cannot be disentangled from the daily-lived experience of taking them (side effects) and the immediate impact on their MS (reducing relapses) and their MS symptoms.

**Figure 3. Temporal disconnection and different RRMS measures**




## 2.2. The meaning of DMT efficacy for people with RRMS

There is no consensus among PwRRMS on the meaning of DMT efficacy. Studies exploring reasons why PwRRMS stop/switch treatments frequently use the term 'DMT efficacy' but do not explore what type of efficacy that is i.e. more relapses, decreased functionality, lesions, or a combination. In fact, some argue that DMT efficacy is a subjective term that depends on individuals' health perceptions [40]. While individual heterogeneity is inherent to RRMS, our review showed that PwRRMS' understanding of DMTs is usually mediated by five factors.

1. Ingrained in double uncertainty. Our review suggested that MS aetiology and the problematic measure of MS progression shape how PwRRMS understand DMTs. MS individual heterogeneity and fluctuating unpredictability can result in PwRRMS interpreting evidence on whether DMTs work as inconclusive. The MS trajectory is often unpredictable and uncertain, and new DMTs which do not necessarily or completely reduce attacks and still lack long-term health outcome data cause additional feelings of uncertainty. Hence, the context in which PwRRMS make treatment choices is defined by this double uncertainty which has a direct impact on their decisions to start, not to start, when to start, delay, continue, stop or switch treatments and which ones to take.

2. Perceived and lived lack of efficacy. Reviewed studies suggested that the majority of PwRRMS perceive and experience lack of DMT efficacy and this is evident in the reasons why people decide to stop them or change to different ones. These are related to two main factors: first, a treatment may not reduce frequency or severity of relapses as expected; second, the time gap between taking the treatment and

experiencing its outcome. The time discordance between the act of taking the treatment (now) and the desired outcome being located in the future can generate an unfounded perception of a lack of efficacy because people cannot attribute relapse-related immediate outcomes to the DMT. There is also a body of evidence that individuals often take decisions biased towards short-term benefits and sub-optimally neglect the long term consequences of their actions [41, 42]. Furthermore, people are not able to really know or think about the counterfactual – that is, they base their judgement of efficacy on what their lived experience is now, having taken the drug. It is impossible to know what their MS could have been like if they had not taken the drug. In addition, in RRMS, physicians are expected to escalate treatments using criteria informed by clinical guidelines [34] and experience. That is, the need to change DMT is inbuilt in the treatment strategy and people living with MS for a few years are likely to have experienced DMT switches attributed to lack of efficacy.

3. DMT as a threat and/or an opportunity to control. When PwRRMS are on DMTs, illness uncertainty is not eliminated because doubts about whether the medication is working remain [1, 38]. In addition, after making a decision to start a DMT that is associated with higher risks and toxicity, PwRRMS worry about potential safety [43]. Despite this accumulation of uncertainties and risks, some PwRRMS use DMTs as a strategy to regain control of their lives [38, 44] rather than hoping for a benign illness course. Our review suggested that deciding not to start/discontinue medication due to uncertainty, may free patients from experiencing DMT side effects and inconvenience, and worrying about risks. PwRRMS interpret and re-interpret DMTs as an opportunity, a threat or both depending on their ever-changing life circumstances, their MS and their previous DMT experiences.

4. DMT impact on wellbeing and MS symptoms. While some PwRRMS experience side effects and others question the effectiveness of their DMTs, they generally see DMTs as having a positive impact on their health and well-being [45, 46]. People, however, perceive the efficacy benefits of different DMTs differently, and often this perception is the leading cause for stopping treatment [47-49]. It also seems that different DMTs provide different levels of satisfaction [50] which can be related to new drugs being perceived as better and the escalation strategy (transition from less risky to more risky treatments) implicitly portraying some drugs as more powerful than others.

DMTs used to be designed to stop or slow MS, however the concept that these drugs can also lead to the improvement has more recently taken hold. Some PwRRMS attribute reduction of daily MS symptoms to DMTs, even though none of the available treatments are developed or licensed to do so [51]. This positive impact on their daily lives is often used as a justification to adhere to treatment and hope positive long-term outcomes. Although some studies reported amelioration of MS

symptoms while on DMTs [44, 52] or improved quality of life [53], according to others, such perceptions are 'misleading' and should be corrected [47, 54]. Although it is important to ensure realistic treatment expectations, patients test and trial medicines by measuring daily the impact on their bodies. Hence, it is not surprising that PwRRMS judge the efficacy of and choose DMTs in terms of their ability to ameliorate the condition experienced daily, rather than their longer-term impact on disease progression.

### 2.3. The influence of decision-making and information acquisition practices in PwRRMS

In fluctuating chronic illnesses like MS, limited trust in medical professionals influences trade-off decisions and is a barrier to escalating medication [55]. Institutional barriers (i.e. consultation time and frequency) to build the necessary trust for shared decision-making are some of the factors preventing a more active patient involvement. Our review suggested that while neurologists' advice seems to be a key driver in PwRRMS treatment choices, patients often lack assistance in understanding the nature and progression of MS and are not sufficiently informed about DMTs.

1. Using doctors' advice. Whereas PwRRMS do tend to carefully consider pros and cons of DMTs before starting treatment, neurologists often play a dominant role in the process [1, 45, 46, 49, 56, 57]. Our review suggested that PwRRMS rarely request their neurologist to prescribe a specific medication and treatment choices are highly shaped by their interactions with neurologists; either by taking their advice into account, or directly following their proposed treatment choice. In this way, the meaning of DMT efficacy for PwRRMS is always mediated by physicians' views (i.e toxicity, efficacy). Clinicians' decisions to suggest or recommend DMTs are guided by emerging clinical guidance [58] that rarely provide space for negotiating psychosocial dimensions of sustaining DMTs in everyday lives. For example, treatment compliance is key and PwRRMS need to be able to manage treatment mode and frequency within their own daily regimen and determine what suits them best - daily tablets, or more infrequent induction therapies, or consider the complexities of PwRRMS who need to travel for work and the complexities of managing injections in those circumstances. In addition, because of short consultation time, medical professionals are rarely able to engage in in-depth discussions about treatment peculiarities other than their impact on the disease progression, side effects or symptoms [56, 59]. As a result, PwRRMS' personal life, family and professional development [60] which also affect DMT decisions are not addressed in time-constrained treatment conversations. This may lead to low adherence, or decisions to stop/skip or switch treatments.

PwRRMS do not feel sufficiently involved in treatment selection and would like to play a more active role in the process [12, 36, 59, 61-63]. It was evident that lengthy and complex diagnostic processes may compromise PwRRMS' trust in their neurologists when discussing DMTs. Some PwRRMS question clinicians' knowledge, expertise and their preference for certain treatments. Furthermore, tension between experienced symptoms and MRI results may encourage people to look for information and expertise elsewhere and this often leads to a delayed treatment start. It was evident that despite this "conditional" trust in clinicians, [46, 64-67], MS specialist clinicians and nurses are most trusted for sources of information. However, PwRRMS often seek to gain a 'full picture' of MS treatments [68], especially in the early stages after the diagnosis [64, 65, 67] by searching out information from other sources, such as leaflets, newspapers, television, books, magazines, and friends, etc. [64, 67]. Information provided by pharmaceutical companies is the least trusted source as PwRRMS question how reliability of information is influenced by marketing and profit- oriented goals [68].

2. Using other PwRRMS' advice. Our review suggested PwRRMS' position that only those who have MS understand what MS is. MS heterogeneity and uncertain clinical evidence encourages the sharing of treatment experiences between PwRRMS. Online communities are increasingly important [64, 66-68] with online social networks [65, 67], MS societies and patient association websites [64, 68] being important to PwMS and their friends and families. Information gathered online enables PwRRMS to be better informed about how the illness and treatments may their lives [64]. This can help preparing for clinician appointments [65], balance out insufficient knowledge about treatment options [56] and to be more actively involved in the decision-making process [64]. Nevertheless, often people find it difficult to filter provided information and apply it to individual cases [65]. Additionally, the utility and accuracy of online information means some patients hear stories of no relevance to their disease and treatments which can be frightening, depressing and generate false hopes [65, 68].

### 3.4. The importance of psychosocial dimensions in DMT decision-making

Our review suggested that the diagnosis of RRMS is marked by intense emotional turmoil and brings with it a number of immediate psychological and social effects that have implications for short and long-term decisions about treatment. From a person-focused perspective, health behaviours like DMT initiation or escalation decisions are the result of complex, multi-faceted representations of illness [69] including: illness itself and the symptoms associated with it; illness time-line;

consequences; and cure/controllability. All these aspects are affected by contextual factors, such as individual social roles and psychological traits.

### 3.4.1. Psychological dimension: Reacting and adapting to disability

People are normally, but not always, diagnosed with MS at a younger age, and learn that their short-term or long-term future could be defined by the illness. There is little agreement in the literature on psychosocial adaptation to the loss of functional ability and the process of 'adaptation'. People with gradually deteriorating and uncertain medical chronic illnesses like MS experience levels of shock, anxiety and depression depending upon the type of temporary impairment experienced at the point of diagnosis. Acceptance seems to require some form of recognition that the condition is likely to worsen, and psychosocial adaptation depends on this recognition as a prior condition.

There is no agreement in the literature on the relationship between individuals' psychological typologies and treatment decision making. In RRMS this heterogeneity may relate to the unique trajectories of the illness. This is also explained by illness representation theory [69], which emphasises the need to look at a patient's everyday beliefs and coping strategies with illness within their social lives rather than their personality to understand their treatment choices. The literature review suggested that PwRRMS, cope with profound stresses related to MS condition and trajectory, such as unknown MS cause, variability of symptoms, ambiguity of diagnosis and treatments, unpredictability of exacerbations and remissions, lack of a cure and presence of impairments. These heterogeneous factors indicate that there are a great number of contextual circumstances that influence whether and how PwRRMS adjust to the illness or continually cycle through sequences of non-adaptive and quasi-adaptive reactions related to the repeated fluctuations of exacerbations and remissions. Furthermore, during the adjustment process to the diagnosis PwRRMS try to maintain as many current and future social roles as possible. Since RRMS operates in a pattern of fluctuating and uncontrolled illness activity, people have to renegotiate their identity based on predicted illness progression, and their everyday lives become shaped around the 'fluctuating normality'. Normality is equated to controlled illness activity, or 'good periods' vs 'bad periods'. So for PwRRMS life is dominated by the fluctuation between disrupted normality and normality [70]. Our review suggested that newly diagnosed PwRRMS often choose treatments depending on their current life circumstances and immediate future plans.

### 3.4.2. The importance of social roles in DMT decision-making

The literature review indicated that PwRRMS' social lives are likely to directly or indirectly influence their DMT decisions. This is important because newly diagnosed PwRRMS are typically young and they do not intend to abandon their current or planned social roles, and fluctuating normality supports these intentions. The adaptation to disability process (typical reactions to disability news are shock, anxiety, denial, depression, internalized anger, externalized hostility, acknowledgment and final adjustment [71]) is based on normalising and sustaining [72] their chosen treatments to proceed with their planned social roles. We identified three key social dimensions impacting DMT decision-making: reproduction, family and social support, and employment.

1. Reproduction. The prevalence of MS among young females is clearly established and recent studies have demonstrated a higher relapse rate in RRMS females compared with males [73]. Women with MS have many concerns related to how pregnancy can affect the illness and its progression, and post-natal ability to care for children related to postpartum relapse and MS symptoms [74-77]. In addition, all DMTs (apart from copaxone) must be stopped before conception and during pregnancy and breastfeeding. In practice, the duration of the interval without treatment is uncertain, since conception periods are unpredictable and breastfeeding experiences vary. Consequently, women are faced with a choice of continuing/starting treatment, or to take the risk of interrupting/delaying treatment while trying to conceive. An important contextual factor in which this decision takes place is that the choice to become a mother is more complex for people with long-term illnesses [78]. Some women with RRMS may take the decision not to conceive because they do not feel capable of 'good mothering', or because- despite the lack of evidence they fear that the child may inherit the illness. With regard to male fertility, the literature is limited, some of the sources [79] reporting general advice to stop taking DMT before insemination.

2. Family and social support. Literature on how family and available social support shape treatment choices of PwRRMS is scarce and none of the reviewed studies directly targeted the relationship between the two. Nevertheless, it was evident that support provided by family and social networks may indirectly shape treatment decisions. For example, family support is important not only in managing the illness but also impact participation in the labour market [80]. Furthermore, PwRRMS who have strong family relationships seem to be more likely to adhere to DMTs [59, 81].

3. Employment. Our review indicated that while DMT use may enable PwRRMS to take up or continue in paid work, treatment-related side effects, and administration and monitoring routines may burden their work-related experiences. This affects the normalisation of the illness and treatment into PwRRMS lives and is likely to play a role in decisions to not start/delay or which DMTs to take. These have to be added

to how the presence and severity of MS symptoms impact participation in labour market. Furthermore, some newly diagnosed PwRRMS do not disclose the illness to their employers and base their treatment decisions on how they may fit their work environment, because they seek to continue positive professional performance or they perceive and experience the workplace as unfriendly [82].

## 4. Discussion

This synthesis and the resulting theoretical insights are summarized in Figure 2 and are an important step in understanding how the contextual, clinical, social and psychological circumstances in which PwRRMS make decisions about whether to initiate DMTs and when to escalate them from a person-focused perspective. We identified a range of factors inherent to RRMS that can matter to patients when they are presented with the range of currently available DMTs at different decision points. Some PwRRMS only ever choose one treatment, and others move through several consecutive treatments escalating and de-escalating associated risks. Making these treatment choices is emotionally demanding, either as a first step onto the treatment pathway when people's understanding and experiences of treatment is impoverished, and/or switching when worrying about the rate of progression of MS. These dimensions are often not raised within usual disease management contexts when considering information to make treatment decisions in the short and long-term.

Treatment decisions are flexible and dynamic, re-interpreted as life unfolds alongside patients' experiences of illness and healthcare. For this reason, while recognising the individuality of patients' experiences, needs and preferences for treatments, this model avoids focusing on DMT characteristics. It does so because DMTs in general are intertwined with uncertainty and risk, and have a different impact on PwRRMS' illness progression and life flow, as well as are negotiated in different social, clinical, psychological and personal contexts of decision-making. Hence why a focus on DMT characteristics regarding illness progression and symptom management, while important, does not give the whole picture of how RRMS treatment decisions are made. Instead, the review draws attention to the importance of concepts other than preferences for illness and symptom management in shaping patients' choices. An emphasis is put on the clinical, institutional and psychosocial contexts in which decisions are made. These interpretations are grounded in concepts of patient journey and illness trajectory, illness representation, disability theory and normalisation of treatment theory.

Our results provide important insights for clinicians and those producing information tools to support PwRRMS treatment decisions because they highlight important

dimensions that need to be acknowledged when communicating with patients (e.g., employment status and work patterns, family plans and obligations, hobbies, future plans, etc.). Furthermore, the results also enable prescribers to consider how these contextual factors shape PwRRMS views of evidence and help them to optimise efforts to support the use of research evidence in treatment decision-making. Finally, this study is an attempt to advance theoretical and conceptual conversations regarding DMT risks and benefits by framing them not exclusively on DMTs attributes or PwRRMS psychological characteristics but instead on how all these factors continuously interact with PwRRMS in the context of their MS and social lives. The theoretical propositions developed here are a first attempt to understand the complex field of PwRRMS treatment decisions. There is a knowledge lacuna on DMT decisions from a person-centred perspective located outside medical treatment decision domain. Furthermore, further investigation is need in male DMT decisions and family planning; and how treatment decisions change overtime depending on individual's personal, social and professional life.

## 5. Conclusion

Patient choice is perceived to start by providing PwRRMS with evidence-based information about diagnostic procedures and treatment regimens [83]. This review has demonstrated that in addition to clinical measures and criteria, contextual factors of patients' everyday lives and realities are equally or even more important. Nevertheless, PwRRMS rarely make treatment decisions independently from their doctors, whose advice is usually founded on medical knowledge and experience with treating other patients. Since treatment decisions are dynamic and change depending on personal life and illness and past treatment experiences, it is crucial to untangle RRMS treatment decisions from the delivery of medical information and understand them as a complex process informed by available but contested medical evidence, patients' lives and their experience with specialist consultants, MS and DMTs.

## Acknowledgments

**Funding:** This work was supported by the MS Society [award number: 30].

## Bibliography


1. Riñon, A., et al., *The MS Choices Survey: findings of a study assessing physician and patient perspectives on living with and managing multiple sclerosis.* Patient Prefer Adherence, 2011. **5**: p. 629-643.
2. Köpke, S., et al., *Steroid treatment for relapses in multiple sclerosis – the evidence urges shared decision-making.* Acta Neurologica Scandinavica, 2004. **110**(1): p. 1-5.
3. Milo, R. and A. Miller, *Revised diagnostic criteria of multiple sclerosis.* Autoimmunity Reviews, 2014. **13**(4–5): p. 518-524.
4. Barnett, M.H. and J.W. Prineas, *Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion.* Annals of neurology, 2004. **55**(4): p. 458-468.
5. Confavreux , C., et al., *Relapses and Progression of Disability in Multiple Sclerosis.* New England Journal of Medicine, 2000. **343**(20): p. 1430-1438.
6. Radomski, A.D., et al., *Decision-making under explicit risk is impaired in multiple sclerosis: relationships with ventricular width and disease disability.* BMC Neurology, 2015. **15**(1): p. 61.
7. Heesen, C., et al., *Risk perception in natalizumab-treated multiple sclerosis patients and their neurologists.* Multiple Sclerosis, 2010. **16**(12): p. 1507-1512.
8. Coles, A.J., *Alemtuzumab Therapy for Multiple Sclerosis.* Neurotherapeutics, 2013. **10**(1): p. 29-33.
9. Havrdova, E., D. Horakova, and I. Kovarova, *Alemtuzumab in the treatment of multiple sclerosis: key clinical trial results and considerations for use.* Therapeutic Advances in Neurological Disorders, 2015. **8**(1): p. 31-45.
10. Riera, R., G.J. Porfírio, and M.R. Torloni, *Alemtuzumab for multiple sclerosis.* The Cochrane Library, 2016.
11. Baroncini, D., et al., *Natalizumab versus fingolimod in patients with relapsing-remitting multiple sclerosis non-responding to first-line injectable therapies.* Multiple Sclerosis Journal, 2016. **22**(10): p. 1315-1326.
12. Heesen, C., et al., *Benefit-risk perception of natalizumab therapy in neurologists and a large cohort of multiple sclerosis patients.* Journal of the Neurological Sciences, 2017.
13. Åsbring, P. and A.-L. Närvänen, *Patient power and control: A study of women with uncertain illness trajectories.* Qualitative Health Research, 2004. **14**(2): p. 226-240.
14. Köpke, S., et al., *Evidence-based patient information programme in early multiple sclerosis: a randomised controlled trial.* Journal of Neurology, Neurosurgery & Psychiatry, 2013.
15. Ormandy, P., *Defining information need in health–assimilating complex theories derived from information science.* Health expectations, 2011. **14**(1): p. 92-104.
16. Webb, E.J., et al., *A Systematic Review of Discrete-Choice Experiments and Conjoint Analysis Studies in People with Multiple Sclerosis.* The Patient-Patient-Centered Outcomes Research, 2018: p. 1-12.
17. Dixon-Woods, M., et al., *Conducting a critical interpretive synthesis of the literature on access to healthcare by vulnerable groups.* BMC medical research methodology, 2006. **6**(1): p. 35.
18. Johnson, M., et al., *Prognostic communication in cancer: a critical interpretive synthesis of the literature.* European Journal of Oncology Nursing, 2015. **19**(5): p. 554-567.

19. Kelly, C.A. and M. Maden, *How do respiratory patients perceive oxygen therapy? A critical interpretative synthesis of the literature.* Chronic respiratory disease, 2014. **11**(4): p. 209-228.
20. Laliberte Rudman, D., et al., *Low vision rehabilitation, age-related vision loss, and risk: a critical interpretive synthesis.* The Gerontologist, 2016. **56**(3): p. e32-e45.
21. Greenhalgh, T., et al., *Beyond adoption: a new framework for theorizing and evaluating nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability of health and care technologies.* Journal of medical Internet research, 2017. **19**(11).
22. Montalban, X., et al., *ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis.* European Journal of Neurology, 2018. **25**(2): p. 215-237.
23. Hutchinson, M., *There is no such thing as a mild MS relapse. The mild relapse is an Anglo-Saxon delusion-Commentary.* Multiple Sclerosis Journal, 2012. **18**(7): p. 930-931.
24. Ross, A.P., J. Halper, and C.J. Harris, *Assessing relapses and response to relapse treatment in patients with multiple sclerosis: a nursing perspective.* International Journal of MS Care, 2012. **14**(3): p. 148-159.
25. Thrower, B.W., *Relapse management in multiple sclerosis.* The Neurologist, 2009. **15**(1): p. 1-5.
26. Halper, J., *The psychosocial effect of multiple sclerosis: the impact of relapses.* Journal of the Neurological Sciences, 2007. **256**: p. S34-S38.
27. Kurtzke, J., *Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS).* Neurology, 1983. **33**.
28. Langeskov-Christensen, D., et al., *Performed and perceived walking ability in relation to the Expanded Disability Status Scale in persons with multiple sclerosis.* Journal of the Neurological Sciences. **382**: p. 131-136.
29. Novakovic, A.M., et al., *Pharmacometric analysis of the relationship between absolute lymphocyte count, and expanded disability status scale and relapse rate, efficacy endpoints, in multiple sclerosis trials.* 2017.
30. Degener, T. *A New Human Rights Model of Disability*. in *The United Nations Convention on the Rights of Persons with Disabilities*. 2017. Springer.
31. Barnes, C. and G. Mercer, *Implementing the social model of disability: Theory and research*. 2004: Disability Press Leeds.
32. Brown, M.G., et al., *Estimating typical multiple sclerosis disability progression speed from clinical observations.* PLoS One, 2014. **9**(10): p. e105123.
33. Fisniku, L., et al., *Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis.* Brain, 2008. **131**(3): p. 808-817.
34. Scolding, N., et al., *Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis.* Practical Neurology, 2015.
35. Rovira, À., C. Auger, and J. Alonso, *Magnetic resonance monitoring of lesion evolution in multiple sclerosis.* Therapeutic Advances in Neurological Disorders, 2013. **6**(5): p. 298-310.
36. Heesen, C., et al., *Decisional role preferences, risk knowledge and information interests in patients with multiple sclerosis.* Multiple Sclerosis, 2004. **10**(6): p. 643-650.
37. Teter, B., et al., *Characteristics influencing therapy switch behavior after suboptimal response to first-line treatment in patients with multiple sclerosis.* Multiple Sclerosis Journal, 2013.
38. Johnson, K.L., et al., *Patient Perspectives on Disease-Modifying Therapy in Multiple Sclerosis.* International Journal of MS Care, 2006. **8**(1): p. 11-18.
39. Thorne, S., et al., *Health Care Communication Issues in Multiple Sclerosis: An Interpretive Description.* Qualitative Health Research, 2004. **14**(1): p. 5-22.

40. Clerico, M., et al., *Adherence to interferon-beta treatment and results of therapy switching.* Journal of the Neurological Sciences, 2007. **259**(1–2): p. 104-108.
41. DellaVigna, S. and U. Malmendier, *Paying not to go to the gym.* American Economic Review, 2006. **96**(3): p. 694-719.
42. Thaler, R.H. and S. Benartzi, *Save more tomorrow™: Using behavioral economics to increase employee saving.* Journal of political Economy, 2004. **112**(S1): p. S164-S187.
43. Miller, C.E., M. Karpinski, and M.A. Jezewski, *Relapsing-Remitting Multiple Sclerosis Patients' Experience with Natalizumab: A Phenomenological Investigation.* International Journal of MS Care, 2012. **14**(1): p. 39-44.
44. Duddy, M., et al., *The UK patient experience of relapse in Multiple Sclerosis treated with first disease modifying therapies.* Multiple sclerosis and related disorders, 2014. **3**(4): p. 450-456.
45. Visser, L.H. and A. van der Zande, *Reasons patients give to use or not to use immunomodulating agents for multiple sclerosis.* European Journal of Neurology, 2011. **18**(11): p. 1343-1349.
46. Salter, A.R., et al., *Patient perspectives on switching disease-modifying therapies in the NARCOMS registry.* Patient preference and adherence, 2014. **8**: p. 971-979.
47. Fox, R.J., et al., *Treatment discontinuation and disease progression with injectable disease-modifying therapies: findings from the north american research committee on multiple sclerosis database.* International Journal of MS Care, 2013. **15**(4): p. 194-201.
48. Patti, F., *Optimizing the benefit of multiple sclerosis therapy: the importance of treatment adherence.* Patient Prefer Adherence, 2010. **4**: p. 1-9.
49. Grytten, N., et al., *Stoppers and non-starters of disease-modifying treatment in multiple sclerosis.* Acta Neurologica Scandinavica, 2013. **127**(2): p. 133-140.
50. Glanz, B.I., et al., *Treatment satisfaction in multiple sclerosis.* International Journal of MS Care, 2014. **16**(2): p. 68-75.
51. Torkildsen, Ø., K.M. Myhr, and L. Bø, *Disease-modifying treatments for multiple sclerosis – a review of approved medications.* European Journal of Neurology, 2016. **23**: p. 18-27.
52. Hemmett, L., et al., *What drives quality of life in multiple sclerosis?* QJM, 2004. **97**(10): p. 671-676.
53. Afolabi, D., et al., *Positive impact of cladribine on quality of life in people with relapsing multiple sclerosis.* Multiple Sclerosis Journal, 2017: p. 1352458517726380.
54. Tobin, W.O. and B.G. Weinshenker, *Stopping immunomodulatory medications in MS: Frequency, reasons and consequences.* Multiple sclerosis and related disorders, 2015. **4**(5): p. 437-443.
55. Fraenkel, L., et al., *Understanding how patients (vs physicians) approach the decision to escalate treatment: a proposed conceptual model.* Rheumatology, 2014. **54**(2): p. 278-285.
56. de Seze, J., F. Borgel, and F. Brudon, *Patient perceptions of multiple sclerosis and its treatment.* Patient preference and adherence, 2012. **6**: p. 263-273.
57. Hanson, K.A., et al., *A cross-sectional survey of patient satisfaction and subjective experiences of treatment with fingolimod.* Patient preference and adherence, 2013. **7**: p. 309-318.
58. Gajofatto, A. and M.D. Benedetti, *Treatment strategies for multiple sclerosis: When to start, when to change, when to stop?* World Journal of Clinical Cases: WJCC, 2015. **3**(7): p. 545.
59. Pietrolongo, E., et al., *Decision-making in multiple sclerosis consultations in Italy: third observer and patient assessments.* PLoS One, 2013. **8**(4): p. e60721.

60. Köpke, S., et al., *Evidence-based patient information programme in early multiple sclerosis: a randomised controlled trial.* Journal of Neurology, Neurosurgery & Psychiatry, 2013: p. jnnp-2013-306441.
61. Heesen, C., et al., *Informed shared decision making in multiple sclerosis—inevitable or impossible?* Journal of the Neurological Sciences, 2007. **259**(1–2): p. 109-117.
62. Giordano, A., et al., *Participation in medical decision-making: Attitudes of Italians with multiple sclerosis.* Journal of the Neurological Sciences, 2008. **275**(1–2): p. 86-91.
63. Kasper, J., et al., *Informed shared decision making about immunotherapy for patients with multiple sclerosis (ISDIMS): a randomized controlled trial.* European Journal of Neurology, 2008. **15**(12): p. 1345-1352.
64. Lejbkowicz, I., et al., *Internet usage by patients with multiple sclerosis: implications to participatory medicine and personalized healthcare.* Multiple sclerosis international, 2010. **2010**.
65. Hay, M.C., et al., *Why Patients Go Online: Multiple Sclerosis, the Internet, and Physician-Patient Communication.* The Neurologist, 2008. **14**(6): p. 374-381.
66. Matti, A.I., et al., *Multiple sclerosis: patients' information sources and needs on disease symptoms and management.* Patient Prefer Adherence, 2010. **4**(3): p. 157-161.
67. Marrie, R.A., et al., *Preferred sources of health information in persons with multiple sclerosis: degree of trust and information sought.* Journal of Medical Internet Research, 2013. **15**(4): p. e67.
68. Synnot, A.J., et al., *Online health information seeking: how people with multiple sclerosis find, assess and integrate treatment information to manage their health.* Health Expectations, 2014. **19**(3): p. 727-737.
69. Brownlee, S., H. Leventhal, and E.A. Leventhal, *Regulation, Self-Regulation, and Construction of the Self in the Maintenance of Physical Health-Chapter12.* 2000.
70. Sanderson, T., et al., *Shifting normalities: interactions of changing conceptions of a normal life and the normalisation of symptoms in rheumatoid arthritis.* Sociology of Health & Illness, 2011. **33**(4): p. 618-633.
71. Livneh, H. and R.F. Antonak, *Reactions to disability: An empirical investigation of their nature and structure.* Journal of Applied Rehabilitation Counseling, 1990.
72. May, C. and T. Finch, *Implementing, embedding, and integrating practices: an outline of normalization process theory.* Sociology, 2009. **43**(3): p. 535-554.
73. Kalincik, T., et al., *Sex as a determinant of relapse incidence and progressive course of multiple sclerosis.* Brain, 2013: p. awt281.
74. Coyle, P.K., *Management of women with multiple sclerosis through pregnancy and after childbirth.* Therapeutic Advances in Neurological Disorders, 2016. **9**(3): p. 198-210.
75. Kosmala-Anderson, J. and L.M. Wallace, *A qualitative study of the childbearing experience of women living with multiple sclerosis.* Disability and Rehabilitation, 2013. **35**(12): p. 976-981.
76. Pakenham, K.I., J. Tilling, and J. Cretchley, *Parenting difficulties and resources: The perspectives of parents with multiple sclerosis and their partners.* Rehabilitation Psychology, 2012. **57**(1): p. 52-60.
77. Payne, D. and K.M. McPherson, *Becoming mothers. Multiple sclerosis and motherhood: A qualitative study.* Disability and Rehabilitation, 2010. **32**(8): p. 629-638.
78. Lappeteläinen, A., E. Sevón, and T. Vehkakoski, *Forbidden option or planned decision? Physically disabled women's narratives on the choice of motherhood.* Scandinavian Journal of Disability Research, 2016: p. 1-11.
79. Alwan, S., et al., *Reproductive decision making after the diagnosis of multiple sclerosis (MS).* Multiple Sclerosis Journal, 2012.

80. Dyck, I. and L. Jongbloed, *Women with Multiple Sclerosis and Employment Issues: A Focus on Social and Institutional Environments.* Canadian Journal of Occupational Therapy, 2000. **67**(5): p. 337-346.
81. Devonshire, V., et al., *The Global Adherence Project (GAP): A multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis.* European Journal of Neurology, 2011. **18**(1): p. 69-77.
82. Frndak, S.E., et al., *Disclosure of disease status among employed multiple sclerosis patients: Association with negative work events and accommodations.* Multiple Sclerosis Journal, 2015. **21**(2): p. 225-234.
83. Heesen, C., et al., *Delivering the diagnosis of MS – results of a survey among patients and neurologists.* Acta Neurologica Scandinavica, 2003. **107**(5): p. 363-368.