

Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS)

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Declaration of Authorship

I, Gurpreet Kaur Reen, hereby declare that this thesis and the work presented in it is entirely my own. Where I have consulted the work of others, this is always clearly stated.

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Abstract

Multiple Sclerosis (MS) patients are faced with complex risk-benefit profiles of disease-modifying drugs (DMDs). It is important that MS patients are able to understand the risks and benefits of DMDs in order to make an informed treatment decision. The goal of the present thesis was to identify the best methods of presenting treatment risks and benefits to improve MS patients' understanding and reduce conflict in their treatment decisions. First, systematic reviews and surveys were conducted to inform the need to improve MS patients' understanding of treatments. Subsequently, three experiments were designed to assess the effect of different presentation methods on MS patients' understanding of hypothetical treatments. Experiment 1 found that treatments presented using non-graphical formats had an effect on patients' understanding ($p < .001$), with numerical frequencies improving understanding the greatest. Understanding of treatments was also affected by presentation using graphical formats ($p < .001$), and was greatest for bar charts and line graphs. Experiment 2 found that presenting treatments using ratios ($p < .001$) and frames ($p < .05$) also affected patients' understanding. Experiment 3 showed that the methods to communicate differences in the risks and benefits of clinical trial groups further had an effect on patients' understanding of treatments ($p < .001$). The BRIMMS protocol was developed by integrating the best presentation methods from Experiments 1-3 and was compared with standard consultation using a randomised controlled trial with crossover design. The BRIMMS protocol improved understanding ($p < .001$) and reduced decisional conflict ($p < .001$) in comparison to standard consultations. In conclusion, some methods to present treatments can improve MS patients' understanding of treatment risks and benefits. The BRIMMS protocol could potentially be implemented into current clinical practice to improve MS patients' understanding and engagement in the decision-making process.

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Chapter 1: General introduction

1.1 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disorder of the central nervous system, affecting over 2.3 million people worldwide (Browne et al., 2014). In the UK alone, approximately 124,000 people were affected with MS at the end of 2010 (Mackenzie, Morant, Bloomfield, MacDonald, & O’Riordan, 2014). The onset of MS typically presents in patients between 20-40 years, with twice as many women affected as men (Ransohoff, Hafler, & Lucchinetti, 2015).

Patients diagnosed with MS are faced with a great deal of uncertainty about their condition. The pathophysiology of MS is not fully known, symptoms of MS can vary considerably between patients and it is not generally possible to predict the course of disease for individual patients with MS.

1.1.1 Pathophysiology of MS

MS is a multifactorial disease with poorly understood aetiology, but is generally thought to result from an interaction between genetic (Sawcer, Franklin, & Ban, 2014) and environmental factors (Belbasis, Bellou, Evangelou, Ioannidis, & Tzoulaki, 2015). Although complex, the major underlying pathological processes involved in the development and progression of MS are considered to be inflammation and neurodegeneration (Compston & Coles, 2008; Sand, 2015).

Inflammation can lead to damage of the myelin sheaths which are the insulating and protective layer surrounding axons of nerves in order to facilitate speedy communication between nerve cells (Compston & Coles, 2008). This damage is termed as demyelination. Consequently, demyelination can disrupt and distort neuronal signals in regions affected by inflammation (Ciccarelli et al., 2014). Initially, this damage can be reversed by the process of remyelination which restores function and conduction of nerve

impulses (Compston & Coles, 2008). However, repeated inflammation can cause lesions to manifest throughout the brain and spinal cord (Ciccarelli et al., 2014; Compston & Coles, 2008; Frohman, Racke, & Raine, 2006).

Continuous demyelination can lead to axon and neuronal degeneration (Compston & Coles, 2008). As MS progresses and new lesions develop, axon and neurodegeneration can accumulate and subsequently lead to permanent neurological disability (Tallantyre et al., 2010). Both white matter (collection of axons which facilitate communication between grey matter and other areas of the body) and grey matter (collection of nerve cells which receive and generate information to the body) in the brain are affected in MS, with disease progression causing more severe damage in the grey matter (Ciccarelli et al., 2014).

1.1.2 MS symptoms

Demyelination and neurodegeneration in MS patients can lead to a wide range of MS symptoms which can vary considerably between people affected by MS. Severity of symptoms can also vary between individuals: whilst some symptoms may require hospitalisation, other symptoms could be so trivial that they do not generally need medical attention (Hauser & Oksenberg, 2006). This heterogeneous symptom profile in MS is related to the corresponding sites that may be damaged in MS patients (Compston & Coles, 2008). The range of symptoms that MS patients experience can be broadly categorised into physical and motor symptoms, fatigue, affective disorders and cognitive impairments (Compston & Coles, 2008; Shahrbanian, Duquette, Kuspinar, & Mayo, 2015; Wood et al., 2013).

1.1.2.1 Physical and motor symptoms in MS

MS patients can experience a range of physical and motor symptoms which usually occur due to neurodegeneration in corresponding sites. For instance, patients may experience unilateral painful loss of vision, scotoma, reduced visual acuity, colour vision

and relative papillary defects due to neuronal damage of the optic nerve (Compston & Coles, 2008). Demyelination in the cerebellum and cerebellar pathway may result in tremor, clumsiness and poor balance; neuronal damage in the brainstem could lead to diplopia, vertigo, impaired swallowing, impaired speech, and in the spinal cord can lead to weakness, stiffness, painful spasms and incontinence. Additional symptoms can also include pain and temperature sensitivity (Compston & Coles, 2008; Hauser & Oksenberg, 2006)

1.1.2.2 Fatigue and affective disorders in MS

Patients can also experience fatigue and affective symptoms of depression and anxiety throughout the course of their disease.

Fatigue

Fatigue is one of the most prevalent symptoms in MS and occurs in approximately 53% to 80% of MS patients (Khan, Amatya, & Galea, 2014; Wood et al., 2013). Fatigue can be defined as a lack of physical and/or mental energy, and can significantly impact the quality of life in MS patients (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Kos, Kerckhofs, Nagels, D'hooghe, & Ilsbroukx, 2008). Fatigue in MS can either be primary which can directly occur due to inflammation and neurodegeneration; or secondary fatigue which can occur due to other peripheral mechanisms in MS such as pain, reduced activity and even depression (Kos et al., 2007). Studies have shown no association of fatigue in MS patients with clinical or demographic variables, such as age, gender, disability, type of MS and disease duration (Kos et al., 2007), which further illustrates the heterogeneous nature of symptoms in MS.

Depression

Depression, or a persistent low mood, is more frequent in patients with MS than the general population, and can affect approximately 18% to 50% of patients (Boeschoten

et al., 2016; Feinstein, Freeman, & Lo, 2015; Jones et al., 2012; Wood et al., 2013). Depression can be a debilitating symptom, substantially affecting individuals' working ability, social relationships and quality of life (Azimian et al., 2014), with elevated suicide rates due to depression in patients with MS (Feinstein et al., 2014). The distinction between depression occurring as a direct result of the inflammation and neurodegeneration process, and depression as a result of being diagnosed with a chronic condition such as MS is yet to be established (Feinstein et al., 2015). There is also a great deal of variability in the prevalence of depression between patients of different gender, ages, disease duration and MS subtype (Jones et al., 2012). However, high depression rates seem to occur concurrently during relapses in MS (Moore et al., 2012).

Anxiety

Anxiety disorders are also very prevalent in MS and occur in about 22% to 45% of MS patients, but are frequently disregarded and undertreated (Boeschoten et al., 2016; Korostil & Feinstein, 2007; Wood et al., 2013). The most common anxiety disorders in MS include panic disorder, obsessive compulsive disorder and generalised anxiety disorder (Korostil & Feinstein, 2007). Similar to depression, symptoms of anxiety can overlap between the somatic manifestations due to degeneration in MS and anxiety about diagnosis of MS as a condition. Some risk factors of anxiety include gender (Korostil & Feinstein, 2007; Jones et al., 2012), limited social support, as well as a co-morbid diagnosis of depression (Korostil & Feinstein, 2007).

1.1.2.3 Cognitive impairments in MS

Cognitive impairments are very prevalent in MS, occurring in approximately 40% to 70% of MS patients (Chiaravalloti & Deluca, 2008; Rao, Leo, Bernardin, & Unverzagt, 1991), with significantly greater impairments appearing in patients with disease duration longer than 5 years (Achiron et al., 2013). Damage to both grey and white matter can contribute to MS-related cognitive impairments (DeLuca, Yates, Beale,

& Morrow, 2015). Cognitive deficits can occur independent of physical disability which can complicate their identification and recognition during the course of the disease (Chiaravalloti & Deluca, 2008). Specifically, MS patients can be impaired on a range of cognitive abilities, including: verbal and visual-spatial memory, information-processing speed and executive functioning, with some degree of comorbidity between these deficits (Chiaravalloti & Deluca, 2008; Fischer et al., 2014; Langdon, 2011).

Memory

The ability to learn and recall information at a later time is defined as long-term memory. MS patients show impairments in remembering both verbal information and visuospatial information (Langdon, 2011). Impairments in memory are one of the most commonly occurring cognitive deficits, appearing in about 40% to 65% of MS patients (Rao et al., 1993). Although it was initially thought that memory could be impaired at the stage of retrieval of information, recent research has established that patients are typically affected during the initial encoding and learning of information, which can subsequently lead to impairments in retrieval of information at a later time (Chiaravalloti & Deluca, 2008; Lafosse, Mitchell, Corboy, & Filley, 2013; Thornton, Raz, & Tucke, 2002).

Information processing speed

Another common cognitive impairment occurs in the speed with which individuals are able to process and manipulate information in their working memory (Chiaravalloti & DeLuca, 2008). MS patients' impairments in processing speed are particularly apparent in their performance across a range of cognitive tasks, which show improvements when patients were allowed more processing time during the task (Bodling, Denney, & Lynch, 2008; Denney, Gallagher, & Lynch, 2011; Denney & Lynch, 2009; Hughes, Denney, Owens, & Lynch, 2013; Langdon, 2011).

Executive functions

Executive functioning refers to complex and higher-order cognitive processes, such as abstract and conceptual reasoning, inhibition, planning and problem-solving, which can also be impaired in MS patients. However, impairments of this type are shown to occur less frequently in MS patients relative to deficits in memory and information processing speed (Chiaravalloti & Deluca, 2008; Denney, Lynch, Parmenter, & Horne, 2004; Drew, Tippet, Starkey, & Isler, 2008).

1.1.2.4 Comorbidity of non-physical MS symptoms

A majority of MS patients commonly experience non-physical symptoms, such as fatigue, affective disorders and cognitive impairments, at the same time.

Many MS patients show symptoms of both anxiety and depression during the course of their disease (Jones et al., 2012; Moore et al., 2012). Both symptoms occurring together has been shown to relate with heightened risk of patients experiencing thoughts of self-harm, somatic complaints and social dysfunction compared to MS patients experiencing anxiety disorders alone (Korostil & Feinstein, 2007). In addition, symptoms of fatigue and depression in MS patients have also been shown to occur together, with improvements in depression generally improving patients' fatigue (Kos, Duportail, D'hooghe, Nagels, & Kerckhofs, 2007). However the strength of this relationship is not always clear or consistent (Feinstein, Magalhaes, Richard, Audet, & Moore, 2014; Hildebrandt & Eling, 2014).

Affective disorders also commonly occur with cognitive impairments in MS (Chiaravalloti & Deluca, 2008; Langdon, 2011). MS patients experiencing depression have consistently shown to perform poorly on tasks of information processing speed (Arnett, Higginson, Voss, Bender, et al., 1999; Arnett, Higginson, Voss, Wright, et al., 1999), but not for tasks assessing long-term memory (Thornton et al., 2002). In addition, a recent longitudinal study of 40 MS patients illustrated that an increase in depressive

mood was related to low performance in tests measuring working memory and executive function (Hildebrandt & Eling, 2014). Similarly, another study found that anxiety disorder, which was experienced by 36% of the clinical sample, was independently related to poor performance on tasks of information processing speed even when controlling for depression and fatigue (Goretti et al., 2014). In terms of fatigue, whilst there exists some evidence of deficit in information processing speed when patients also experience fatigue (Andreasen, Spliid, Andersen, & Jakobsen, 2010), fatigue is generally not associated with poor performance on cognitive tasks (Bailey, Channon, & Beaumont, 2007; Chiaravalloti & Deluca, 2008; Hildebrandt & Eling, 2014). However, it has been proposed that MS patients may experience fatigue whilst conducting extensive cognitive assessments (Langdon, 2011), which may indirectly affect cognitive performance on tasks albeit to a lesser degree than affective symptoms of MS. Thus, whilst patients that experience either anxiety or depression show impairments in cognitive performance, the findings are mixed in regards to patients who experience only fatigue.

1.1.3 MS subtypes

Severity and frequency of MS symptoms is generally dependent on the rate of neurodegeneration in patients. Due to the variability in the rates at which the disease progresses between patients, 4 different subtypes of MS have been proposed: clinically-isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS).

At the very first stage of the disease, approximately 80% of MS patients can experience an acute attack of demyelination, also known as a relapse. At this stage, an independently occurring relapse is categorised as a CIS subtype (Compston & Coles, 2008). If this relapse is accompanied by abnormalities of the white matter, the possibility of a second episode of demyelination can increase.

Multiple attacks of demyelination, or relapses, can be classified into the most commonly occurring RRMS subtype (Fisniku et al., 2008). RRMS is typically defined as multiple acute relapses followed by a period of clinical stability in which full or partial recovery is possible (Sand, 2015). Given this process of recovery, most patients only experience moderate disability at this stage of the disease (Scalfari, Neuhaus, Daumer, Muraro, & Ebers, 2014). RRMS may also be characterised as being active or not active, with activity referring to new or enlarging lesions shown through MRI and/or clinical relapses occurring at least annually (Lublin, 2014).

A minority of patients (<10%) may develop individual lesions in the brain and spinal cord independent of any relapses, categorised as the PPMS subtype (Polman et al., 2011; Ransohoff et al., 2015; Sand, 2015). In these patients, severe disability accumulation can occur at the onset of the disease (Ransohoff et al., 2015).

Overtime, patients with RRMS can also have accumulation of disability as post-relapse recovery remains incomplete and there is a gradual progression of neuronal degeneration (Rovaris et al., 2006; Sand, Krieger, Farrell, & Miller, 2014). Patients at this stage are classified as the SPMS subtype. To date, there are no clear pathological criteria to determine when RRMS transitions to SPMS (Rovaris et al., 2006) and the disease course is largely unpredictable in individual cases (Sand et al., 2014). This unpredictability was shown in a recent study by Scalfari and colleagues (2014) which attempted to determine a clinical portfolio of untreated individuals with MS transitioning from RRMS to SPMS. Approximately 66% patients progressed to the SPMS stage of the disease between 1 to 36 years of being diagnosed with RRMS, with the probability of transitioning from RRMS to SPMS increasing by 9% every 5 years. Only a few variables were found to reliably predict the time taken for progression of disease, that is: male sex, older age at onset and a high number of early relapses. However, the type and number of

neurological systems involved at onset were not found to affect the probability of MS becoming progressive (Scalfari et al., 2014).

1.1.4 Summary

MS patients are faced with a great deal of uncertainty throughout their disease. MS patients can experience a wide range of symptoms which may be either physical, affective or cognitive. It is not always possible to determine the reason for disease onset or the rate at which the disease will progress for an individual. Treatments are geared towards slowing down the progression of disease by reducing the rate of relapses in MS patients.

1.2 Disease-modifying drugs in MS

Although there is no cure for MS at present, extensive research and rapid advances in the last two decades have increased treatment options that can delay the progression of disease in the form of disease-modifying drugs (DMDs) (English & Aloï, 2015; Wingerchuk & Weinshenker, 2016; Winkelmann, Loebermann, Reisinger, Hartung, & Zettl, 2016). Current preventive DMDs for MS primarily target relapses, reducing their frequency and severity by modulating or suppressing immune function, which can subsequently delay the progression of disease and reduce disability (Winkelmann et al., 2016). For this reason, DMDs are not suitable in patients who do not experience relapses (i.e. patients with the PPMS or SPMS subtype) (Wingerchuk & Weinshenker, 2016).

Currently, 14 DMDs have been approved by the Food and Drug Administration (FDA) for the treatment of MS in the US (Wingerchuk & Weinshenker, 2016). Of these, only some DMDs are offered to patients at the very first stage after RRMS diagnosis and are termed “first-line treatments”. These DMDs are generally less aggressive, with smaller risk profiles but with modest efficacy. At present, the following drugs are usually offered to patients as first-line treatments in Europe: interferon betas (5 drugs), glatiramer

acetate (2 drugs), dimethyl fumarate, and teriflunomide (Dorr, Paul, Dörr, & Paul, 2015; Winkelmann et al., 2016). The remaining drugs are offered to patients with highly active disease and who do not show improvements with first-line choices. These drugs are often more aggressive than first-line treatments but also offer higher efficacy. DMDs that are generally used at these later stages as second-line and third-line treatments in Europe include: fingolimod, mitoxantrone, natalizumab, alemtuzumab and daclizumab (Dorr et al., 2015; Scolding et al., 2015; Wingerchuk & Weinshenker, 2016). The decision to transition patients from first-line treatments to other DMDs is not always clear, and is usually dependent on the patient's disease activity, tolerability to DMDs and the risk-benefit profiles of treatments (Dorr et al., 2015).

To demonstrate the complex risk-benefit profiles of DMDs in first-line, second-line and third-line treatments, the following section provides detailed examples of some commonly prescribed DMDs for MS patients in the UK.

1.2.1 Interferon betas

Interferon betas (IFN- β) are first-line immunomodulatory drugs with complex mechanism of action and have been used as treatments in MS for over 20 years, not including the pegylated IFN- β which was licensed only recently (Carrithers, 2014; Winkelmann et al., 2016). IFN- β are administered by injections, with frequency of injections varying depending on which of the five interferon beta drugs are prescribed to patients (Wingerchuk & Weinshenker, 2016; Winkelmann et al., 2016).

IFN- β s have been established as moderately successful by clinical placebo-controlled trials. IFN- β s consistently show a reduction in annual rate of relapses by approximately one third compared to patients taking a placebo. IFN- β s also show moderation in the development of new brain lesions, as well as a reduction in disability (Calabresi et al., 2014; IFNB Multiple Sclerosis Group, 1993; Jacobs et al., 1995; Jacobs et al., 2000; Johnson et al., 1995; Panitch et al., 2002).

The most frequently reported side-effects for IFN- β s include injection-site reactions, flu-like symptoms and fatigue. Patients may also experience adverse risks when taking IFN- β s, such as: leukopenia and worsening of depression (Bandari, Sternaman, Chan, Prostko, & Sapir, 2012; Jacobs et al., 1995; Jacobs et al., 2000; Johnson et al., 1995; Winkelmann et al., 2016). Recently, there has also been a reported case of progressive multifocal leukoencephalopathy (PML) in a patient treated with IFN- β (Lehmann, Kruger, Fink, & Schroeter, 2015). PML is a severe infection affecting the CNS and is associated with high rates of mortality and serious disability. However, it has been suggested that the patient's other underlying disease likely caused the PML rather than administration of IFN- β treatment (Winkelmann et al., 2016).

Given the long-term treatment history of IFN- β s and the low frequency of adverse risks, IFN- β s are commonly offered as low invasive treatments to newly diagnosed patients despite only being moderately effective.

1.2.2 Dimethyl fumarate

Dimethyl fumarate is another first-line agent with immunomodulatory effects which can be taken orally. This treatment was licensed for use in MS by the FDA in 2013 (English & Aloï, 2015).

Two recent and large clinical trials showed an approximate 50% reduction in annual relapse rate after taking dimethyl fumarate for 2 years (Fox et al., 2012; Gold et al., 2012). Disability progression and number of lesions shown in an MRI scan was also significantly reduced in patients taking dimethyl fumarate when compared to a placebo group (Gold et al., 2012). Similar rates of efficacy were also evident in another clinical trial for patients taking dimethyl fumarate, compared with patients taking the first-line treatment glatiramer acetate (Fox et al., 2012). Improvements in perceived health status and quality of life were also reported by patients taking dimethyl fumarate (Kappos et al., 2014).

Common side-effects of dimethyl fumarate include flushing and gastrointestinal symptoms, such as diarrhea, nausea and upper abdominal pains. Minor infections were reported in about 55-68% of MS patients, generally affecting the upper respiratory tract or urinary tract (Fox et al., 2012; Gold et al., 2012). Infections were classified as severe in about 2% of MS patients in both clinical trials (Fox et al., 2012; Gold et al., 2012). Another concern in dimethyl fumarate is that of PML which has been reported in 4 patients as of November 2015 (Winkelmann et al., 2016). For this reason, new monitoring requirements have been proposed to reduce the risk of developing PML in patients taking dimethyl fumarate (Winkelmann et al., 2016).

In comparison to interferons and glatiramer acetate, dimethyl fumarate can provide higher rates of efficacy in MS patients but also with somewhat higher rates of risks.

1.2.3 Fingolimod

Fingolimod was the first approved oral medication for MS by FDA in 2010 (English & Aloï, 2015). Although formally approved as a first-line treatment, fingolimod is usually offered to patients as a second-line treatment in Europe (Dorr et al., 2015; Winkelmann et al., 2016).

In a double-blind randomised clinical trial of 1033 RRMS patients, fingolimod showed a reduction in annual relapse rate by up to 67% when compared to patients taking a placebo (Kappos et al., 2010). Moreover, the risk of disability progression was significantly reduced for patients taking fingolimod (Kappos et al., 2010). Another clinical trial was conducted with 1292 RRMS patients to compare the efficacy of fingolimod with one of the IFN- β treatments (Cohen et al., 2010). Patients taking fingolimod showed a reduction in annual relapse rate by approximately 74%. However, there was no significant delay in the risk of disease progression following fingolimod in comparison to IFN- β treatment (Cohen et al., 2010). Both trials also showed significant

reductions in the number and volume of lesions in the brain (Cohen et al., 2010; Kappos et al., 2010).

Frequently reported side-effects for fingolimod include headaches, nausea, back pain, diarrhea and fatigue (Cohen et al., 2010; English & Aloï, 2015; Kappos et al., 2010). Adverse risks associated with fingolimod include high liver enzymes, herpes infection and cardiac risk of bradycardia (Braune, Lang, & Bergmann, 2015; Cohen et al., 2010; Fox et al., 2014; Kappos et al., 2010; Winkelmann et al., 2016). Patients taking fingolimod may therefore need to be monitored closely for the development of these adverse risks. For example, due to the severe risk of bradycardia, patients' pulse and blood pressure must be monitored for 6 hours following administration of the first dose (English & Aloï, 2015) or if taking the drug after a break of two weeks (Bandari et al., 2012). Another severe risk associated with fingolimod is that of varicella zoster virus (VZV), a serious viral infection present in about 11 patients out of 1000 patients taking the DMD, compared to 6 patients out of 1000 patients taking the placebo (Arvin et al., 2014). Two cases of PML infection have also been reported in MS patients taking fingolimod (Winkelmann et al., 2016).

In general, fingolimod offers superior efficacy for reduction in relapse rates but with a number of severe risks which requires regular monitoring of patients taking the drug.

1.2.4 Natalizumab

Natalizumab is another second-line MS treatment administered by intravenous injection to RRMS patients, and was approved by the FDA in 2004 (Carrithers, 2014; Wingerchuk & Weinshenker, 2016).

The robust efficacy of natalizumab has been demonstrated in a number of clinical trials; MS patients taking natalizumab had 68% reduction in relapse rate after 1 year, with up to 83% reduction in accumulation of new or enlarging lesions when compared to

patients taking the placebo (Miller et al., 2009; Polman et al., 2006). Around 42% of RRMS patients also show reduction in disability when compared to patients taking the placebo. Significant improvements have also been reported on quality-of life measures (Rudick, 2011).

Despite its efficacy, natalizumab is usually reserved for patients who do not show delays in disease progression with first-line treatments and have a highly active disease (Carrithers, 2014; Dorr et al., 2015). This is due to the number of adverse risks that have been associated with natalizumab, such as pneumonia, neurosepsis, appendicitis and viral infections (Polman et al., 2006; Winkelmann et al., 2016). Another severe risk that patients develop following natalizumab is that of PML (Keegan, 2011; Kleinschmidt-DeMasters, & Tyler, 2005; O'Connor & Kremenchutzky, 2015). As of 2012, some 212 patients out of 99,571 patients developed PML after taking natalizumab; 22% of patients died and 40% of those that survived developed a severe disability after 6 month of follow-up (Bloomgren et al., 2012). Due to the severity of PML, natalizumab was temporarily discontinued until 2006 and was brought back into the market under the condition that patients are closely monitored and all cases of PML are reported (Rudick, 2011). With regular reporting and research into natalizumab-associated PML, three risk factors of PML have been identified: status of a JC virus, duration of natalizumab treatment and prior use of DMDs (Bloomgren et al., 2012). Patients taking natalizumab who are negative to anti-JC virus antibodies present the lowest risk of developing the condition, at 0.09 cases or fewer per 1000 patients. However, if patients present with all possible risk factors, i.e. positive to anti-JC virus antibody, extensive use of other DMDs and having taken natalizumab for over 24 months, the risk of PML can reach approximately 11.1 cases per 1000 patients (Bloomgren et al., 2012).

Overall, natalizumab can offer very high efficacy in RRMS patients who continue to show disease activity with first-line treatments. However, due to its high risk

profile, it is essential that patients taking this DMD are regularly monitored for their risk of developing PML and other serious infections.

1.2.5 Summary

DMDs can reduce the rate of relapses and delay progression of MS especially for patients with the RRMS subtype. DMDs are typically offered in two stages to MS patients. Patients are first offered DMDs with lower associated risks, but these are only moderately effective. However, tolerability to DMDs may differ considerably between patients. For this reason, some patients are transitioned to other first-line or later-line treatments if the disease continues to be active. Second- and third-line treatments are more effective, but also have higher associated risks. The risk-benefit profiles among DMDs at the same stage can also vary.

1.3 Patient understanding of treatment information

It is important that patients are able to understand the complex risk and benefit information of DMDs in order to better engage in decision-making about treatments and have increased adherence to the treatment they initiate.

1.3.1 Patient-centered care and shared decision-making

A patient-centred approach has been advocated for use in healthcare systems around the world (World Health Organisation, 2000), and is currently implemented in the UK National Health Service (NHS) (National Health Service, 2005). Patient-centred approach refers to involving patients in all healthcare decisions and to better acknowledge patients' experiences of their condition (Barry & Edgman-Levitan, 2012; Gerteis, Edgman-Levitan, Daley, & Delbanco, 1993). In fact, patients with MS actually prefer more control in their healthcare decisions (Heesen, Kasper, Segal, Köpke, & Mühlhauser, 2004). This is in contrast to the paternalistic approach, which advocates that health professionals decide what is best for the patient (i.e. patients take on a more passive role

in treatment decisions). However, this approach is now considered outdated in the context of modern healthcare services (Coulter, 1999).

According to the patient-centred approach, patients should be incorporated in decisions about the treatments that are most suitable for their disease course and be encouraged to play an active role in the deliberation process (Michie, Miles, & Weinman, 2003). This method of making decisions between patients and health professionals is referred to as the shared decision-making approach (Barry & Edgman-Levitan, 2012; Charles, Gafni, & Whelan, 1997, 1999; Godolphin, 2009; Stiggelbout et al., 2012). This approach is particularly suited to conditions where the disease course is unpredictable and there are variety of possible treatments available, each with different risk-benefit profiles, but no preferable treatment option (Charles et al., 1997, 1999; Heesen, Köpke, Solari, Geiger, & Kasper, 2013; Wagner & Groves, 2002). Moreover, shared decisions are more effective when conducted over a longer term, such as in chronic conditions like MS, in order for healthcare professionals and patients to fully engage with the decision-making process (Joosten et al., 2008).

There are several key features that are involved in the shared decision-making approach. One key feature is the clear and accurate sharing of information between health professionals and patients, often considered a prerequisite for effective shared decision-making (Barry & Edgman-Levitan, 2012; Charles et al., 1997, 1999; Elwyn, Frosch, & Rollnick, 2009; Makoul & Clayman, 2006; Quill & Brody, 1996). Patients can share their personal preferences and values with health professionals, for instance by conveying the treatment risks and benefits they will be willing to accept (Charles et al., 1999; Godolphin, 2009; Makoul & Clayman, 2006). This is crucial, given that patients' attitudes towards risks are strongly related with the treatments they choose to initiate (Fraenkel, Bogardus Jr., & Wittink, 2003; Prosser, Kuntz, Bar-Or, & Weinstein, 2002). It is also important that health professionals share clear and accurate treatment information

with patients. Provision of information to patients relies on some autonomy on the part of patients, without advocating that patients be left completely burdened by treatment decisions; a type of approach which is not generally recommended (Deber, Kraetschmer, Urowitz, & Sharpe, 2007; Levinson, Kao, Kuby, & Thisted, 2005; Parascandola, Hawkins, & Danis, 2002). Information shared by health professionals can consist of: explaining the reasons for making a treatment decision, presenting all available treatment options, discussing and explaining the risks and benefits of all available options, and sharing personal knowledge and recommendations about treatments (Makoul & Clayman, 2006; Thomson, 2013). However, in order for this information to be used effectively by patients during decision-making, it is essential that patients are able to fully understand the information they receive (Barry & Edgman-Levitan, 2012; Charles et al., 1997, 1999; Elwyn et al., 2009; Godolphin, 2009).

1.3.2 Treatment adherence and discontinuation

Misunderstanding treatment information can impact how patients adhere to treatments. This is particularly problematic for a chronic condition such as MS, as medications need to be adhered to for long periods of time in order to effectively reduce disability and delay progression of disease (Winkelmann et al., 2016). Increased adherence to DMDs can further lead to better clinical outcomes, such as lower risks of being hospitalised and fewer rates of relapses (Halpern, Agarwal, Dembek, Borton, & Lopez-Bresnahan, 2011; Steinberg, Faris, Chang, Chan, & Tankersley, 2010; Tan, Cai, Agarwal, Stephenson, & Kamat, 2011).

MS patients are likely to discontinue treatments if they cannot tolerate the side-effects and risks associated with their treatment (Giovannoni, Southam, & Waubant, 2012; Jernas, Wencel, Wiak, Bieniek, & Bartosik-Psujek, 2016; Patti, 2010; Vangeli et al., 2015; Wicks et al., 2015), if disability increases following treatment (Rio et al., 2005), or if patients perceive their medication be less effective than when they began the

treatment (Menzin, Caon, Nichols, White, & Friedman, 2013; Vangeli et al., 2015). In order to improve treatment adherence, it has therefore been suggested that patients are provided with clear and accurate information about treatment risks and benefits during the decision-making process (Petrie, Perry, Broadbent, & Weinman, 2012; Smrtka, Caon, Saunders, Becker, & Baxter, 2010; Twork et al., 2007).

In sum, adherence to DMDs is important for patients to observe benefits in their condition. Given that MS patients discontinue treatments due to high risks and poor efficacy, it is reasonable to expect that accurately understanding the risks and benefits of DMDs can lead to realistic expectations of treatment effects and subsequently improve adherence to treatment.

1.3.3 Criteria for providing evidence-based patient information

Patient understanding of DMD information can be facilitated by providing additional information to supplement, reinforce and improve the treatment information provided by clinicians during consultations (Bunge, Mühlhauser, & Steckelberg, 2010). In order to ensure patients are able to understand the information they receive, treatment information should be presented in an accessible, reliable and comprehensible manner. A number of recommendations have been made to ensure clear and accurate treatment information is provided to patients. This includes: using plain and standardised written language (Fagerlin, Zikmund-Fisher, & Ubel, 2011), providing unbiased information about the risks and benefits of treatments (Edwards, Elwyn, & Mulley, 2002; Paling, 2003), and employing visual aids alongside numerical information (Bunge et al., 2010; Edwards et al., 2002; Fagerlin et al., 2011; Paling, 2003).

MS patients' understanding of the risks and benefits of DMDs may improve by implementing recommendations from the scientific literature. However, in order to determine whether these recommendations actually improve understanding and lead to

informed treatment decisions in MS, these methods should be empirically tested with the MS population.

1.3.4 Summary

Shared decision-making is crucial within a patient-centred approach in healthcare and is often used in the context of decision-making about treatments in chronic condition such as MS. A prerequisite of shared decision-making requires that patients communicate their preferences for treatments to health professional, and health professionals provide clear and accurate risk and benefit information about all available treatment options. It is essential that patients understand the information they receive in order to make decisions that correspond with their personal preferences. Misunderstanding treatment information and initiating treatments that do not reflect patient's preferences can subsequently affect patients' adherence to treatment. Patient understanding can be facilitated by presenting treatment information using methods that can be effectively understood.

1.4 Thesis summary

MS patients are faced with a high degree of uncertainty about their disease course and complex risk-benefit profiles of treatments which can potentially delay the progression of disease. Understanding the risks and benefits of DMDs is important to allow patients to make informed treatment decisions in line with personal preferences and adhere to treatments they initiate. However, it is likely that the complexity of DMD risk-benefit profiles can increase difficulty in understanding treatment information. Fatigue, affective and cognitive symptoms of MS may further make MS patients more susceptible to misunderstanding treatment information. Following guidelines available in the literature, it is likely that patient understanding can be facilitated by presenting information using comprehensible methods.

The following research proposes to develop an integrated intervention known as the Benefit and Risk Information for Medications in Multiple Sclerosis (BRIMMS)

protocol to maximise understanding of DMD risks and benefits and reduce conflict their treatment decisions. This protocol will be developed in light of the available literature and empirical studies conducted with MS patients about the best methods of presenting DMD information. An overview of the thesis is provided below and is also presented in figure 1.1.

First, chapter 2 will assess the literature on MS patients' understanding and preferences of DMD risks and benefits using a systematic review methodology. A second systematic review will also be conducted to assess efficacy of current interventions that have been designed to maximise MS patients' understanding of treatment information.

Following this, chapter 3 will employ surveys with both MS patients and MS healthcare professionals to determine how MS patients currently understand DMD information and how treatment information is provided to patients in the UK.

Chapters 4-6 will empirically evaluate different methods of presenting treatment risk and benefit information to MS patients. Specifically, chapter 4 will identify the best numerical and graphical formats of providing information, chapter 5 will identify the best numerical ratios and frames to present information and chapter 6 will explore how differences between risks and benefits from a clinical trial can be communicated to MS patients in an accessible manner.

Findings from all chapters will subsequently inform the development of the evidence-based BRIMMS protocol. Chapter 7 will empirically evaluate the effectiveness of the BRIMMS protocol to maximise MS patients' understanding and reduce conflict in treatment decisions by comparing this to standard methods of providing treatment information in healthcare using a randomised-controlled methodology.

Finally, chapter 8 will discuss limitations of the current thesis, future suggestions and general implications of the BRIMMS protocol to improve understanding in MS patients about DMDs.

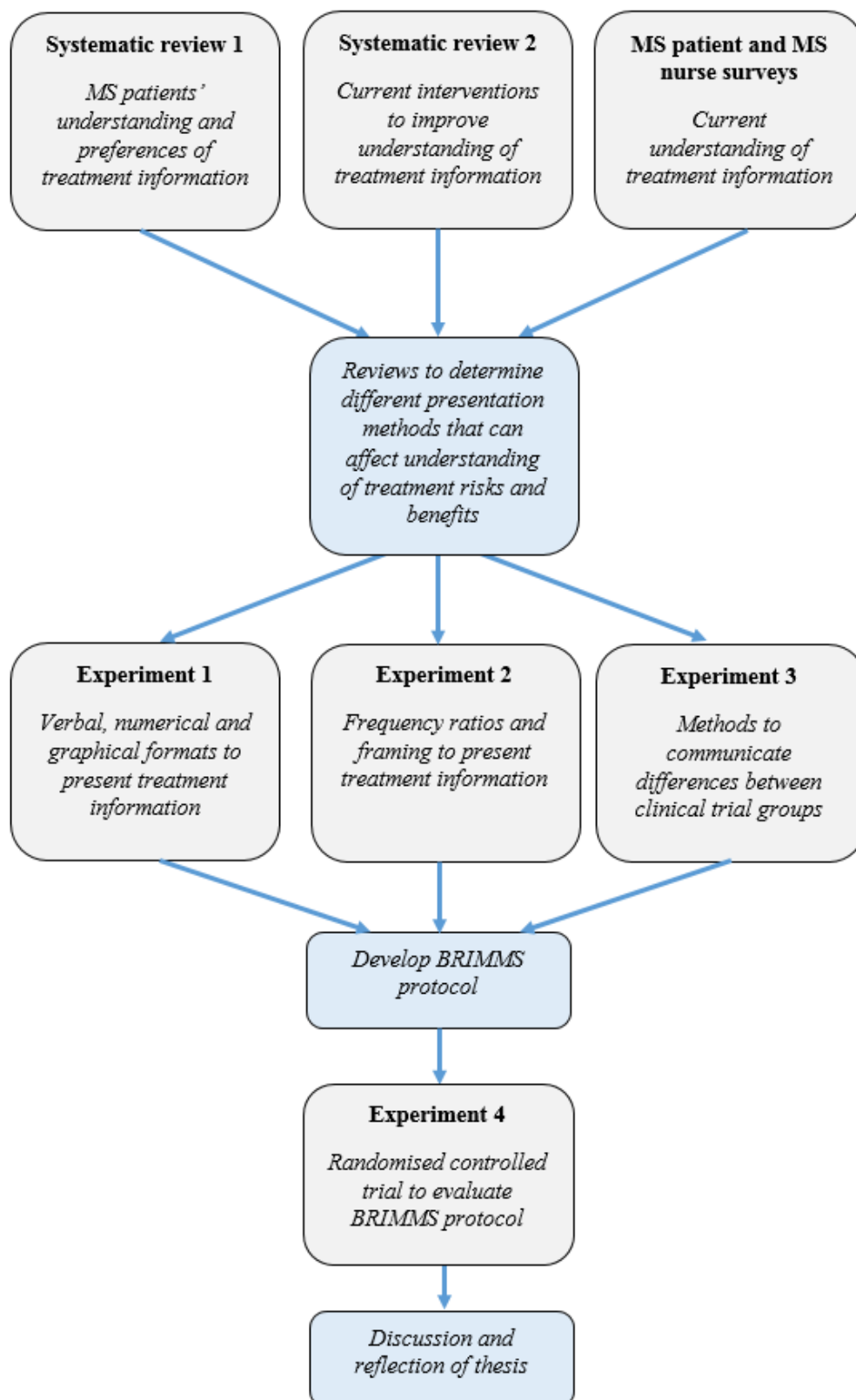


Figure 1.1 Thesis overview

Chapter 2: Systematic reviews

2.1 Introduction

MS patients are faced with complex risk-benefit profiles of DMDs when making decisions about the best course of treatment (see section 1.2 for review about DMDs). It is important that MS patients are able to understand these risks and benefits to ensure treatment decisions are informed and in line with personal preferences, which can likely improve adherence to treatments and engagement with the decision-making process (Barry & Edgman-Levitan, 2012; Rieckmann et al., 2015; Smrtka et al., 2010).

The current chapter sought to conduct two systematic reviews in order to evaluate MS patients' understanding of the risks and benefits of DMDs: first, by systematically reviewing current status of MS patients' understanding and preferences of DMD risks and benefits, and second, by systematically reviewing interventions that have been designed to improve MS patients' understanding of DMD risks and benefits.

2.2 Systematic review 1: MS patients' understanding and preferences of DMDs¹

The first systematic review was conducted to explore MS patients' current understanding and preferences for risks and benefits of treatments; factors important for effective decision-making. The primary aim of this review was to evaluate MS patients' understanding of risk and benefit information for DMDs within standard healthcare. The secondary aim was to identify MS patients' preferences for treatment risks and benefits, and assess to what extent these preferences informed MS patients' treatment decisions.

¹ This systematic review has been published as: Reen, G. K., Silber, E., & Langdon, D. W. (2017). Multiple sclerosis patients' understanding and preferences for risks and benefits of disease-modifying drugs: A systematic review. *Journal of the Neurological Sciences*, 375, 107–122 (see appendix 1).

2.2.1 Method

2.2.1.1 Systematic literature search

The systematic literature search was initially carried out in February 2015 and was subsequently updated for publication in February 2016. The search for studies was conducted in PubMed, Embase and Google Scholar using specific search terms for both study aims (see table 2.1). After removing duplicate entries, a total of 889 records were identified.

Table 2.1 Search terms for Systematic review 1: Primary aim and secondary aim

Search terms
(Multiple AND Sclerosis)
AND
(patients OR people OR persons OR patient)
AND
(risk OR benefit OR side effect)
AND
(treatment OR medication OR therapy OR medicine OR medical OR therapies OR therapeutics OR Pharmaceutical preparations)
AND
(perception OR understanding OR comprehension OR awareness OR knowledge OR information OR communication OR preference OR decision-making)

Studies were eligible for inclusion if they were: in English, with human adults and of any study design. Studies with patients of any MS disease subtype were included. No date restriction was applied. For both aims, studies were included if they had some evaluation of disease-modifying drugs and when the evaluations focused on patients with MS.

Studies were excluded if they discussed medications for MS symptom management or complementary medicines. Studies with evaluation of patients' understanding of disease-modifying drugs post educational intervention was not included.

However, baseline measures prior to any educational intervention were eligible for inclusion in the present review. Studies that assessed MS patients' understanding of other areas in MS, including diagnosis and prognosis, were excluded. Studies focusing only on patients' adherence to DMDs were also excluded.

Following screening of titles and abstracts, 835 records were excluded. Full texts were subsequently accessed. Studies that were considered relevant from screening references were also identified. Thus, data was extracted for a total of 58 full-texts, and studies were included into the final review if inclusion and exclusion criteria were met (see figure 2.1).

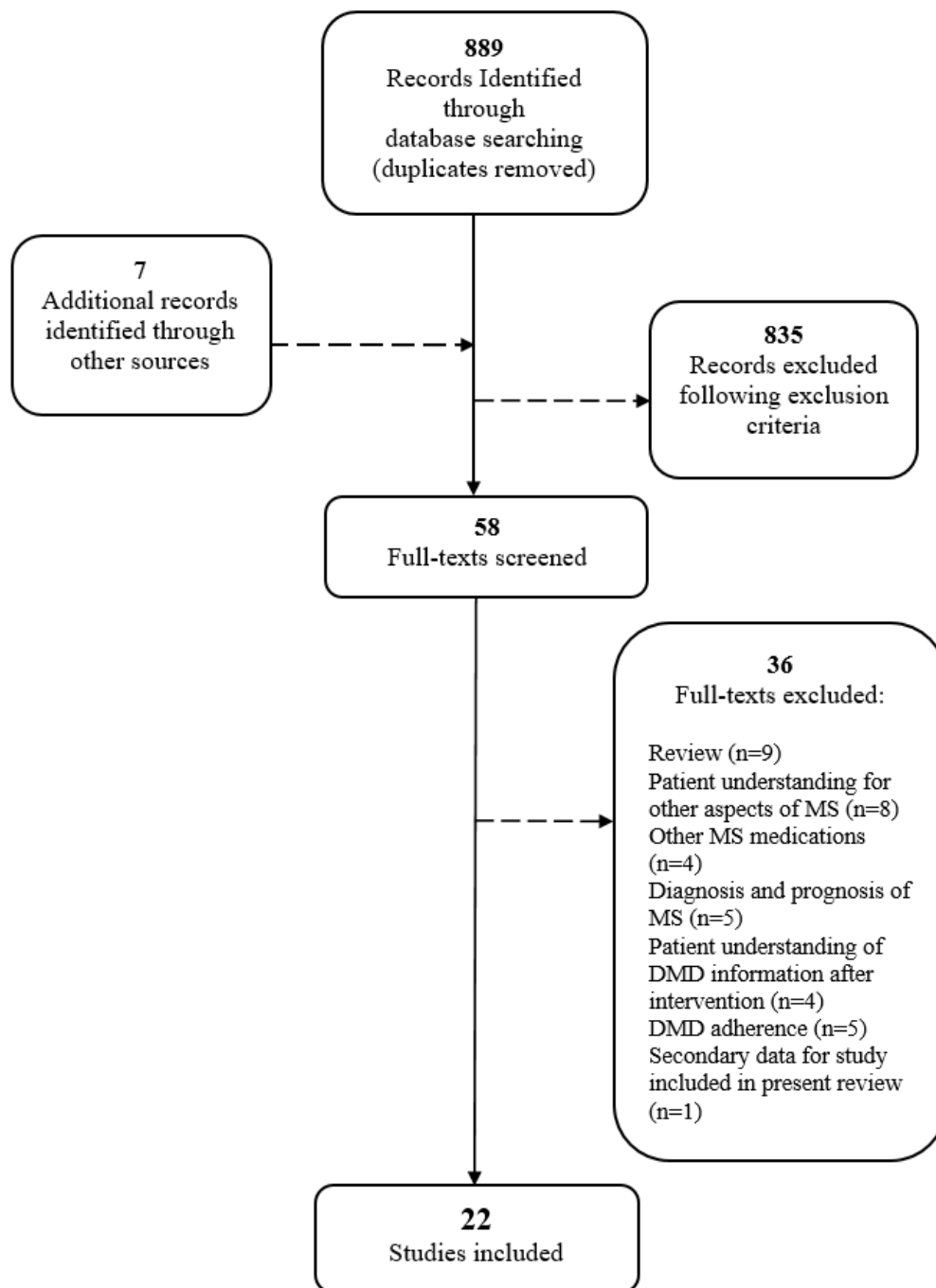


Figure 2.1 Flow diagram for studies included in systematic review 1: Primary aim and secondary aim

2.2.1.2 Data extraction

Data extraction was carried out by one reviewer (GR) using data extraction forms specifically designed for the current review, and was verified by another (DL). Any discrepancies were resolved by discussion. After extraction of full texts, a total of 22

studies were included into the final review across both study aims. One study had relevant findings for both the primary aim and secondary aim. Thus, 14 studies were included into the primary aim and 9 studies were included into the secondary aim.

Baseline characteristics of MS patients were extracted from all 22 studies, which covered age, the type of MS and current DMD status. Since very few studies exclusively assessed understanding or preferences of treatment risks and benefits in MS, studies with any evaluation of either aim were retained.

For the primary aim, any data available on understanding of treatment risks or benefits, or understanding of the treatment overall, was retained. Only understanding of information about real DMDs was incorporated into this aim. This information sometimes existed as baseline measures in intervention studies. Both self-report and objective measures were included for review, in addition to themes from qualitative studies.

For the secondary aim, patients' preferences for treatment risks only, treatment benefits only and a combined trade-off between treatment risks and benefits were considered. Preferences for treatment risks and benefits were defined as patients' attitudes towards risks and benefits, the levels of risks and benefits MS patients were willing to accept, or MS patients' perception of their current DMD. Preferences for risks and benefits of both real DMDs and hypothetical treatment scenarios were included in this aim, providing that hypothetical risk-benefit scenarios were relevant to MS. Similar to the primary aim, information from self-report and objective measures were discussed.

Relevant data was obtained from numerical information in texts, tables, graphs, and relevant statistical analysis. For qualitative studies, relevant themes were extracted and discussed. Medication names are given as reported in each study. Due to the heterogeneity of the studies in the present review, a narrative synthesis was conducted.

2.2.1.3. *Quality assessment*

All studies in this review were examined independently for quality by two reviewers (GR and DL) using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies (Thomas, Ciliska, Dobbins, & Micucci, 2004). This particular tool was chosen because it is often used to evaluate different types of quantitative studies in the health care setting (Armijo-Olivo, Stiles, Hagen, Biondo, & Cummings, 2012), it has high inter-rater reliability (Armijo-Olivo et al., 2012) and is considered ideal for use in systematic reviews (Deeks et al., 2003). As per the tool, the final quality rating was derived from the rating of 6 measures.

The Critical Appraisal Skills Programme (CASP) tool was used to appraise the quality of qualitative studies in this review. This tool was chosen as it has often been recommended for reviewers (Hannes, Lockwood, & Pearson, 2010) and was previously used in other systematic reviews (Campbell et al., 2003)

2.2.2 Results of primary aim

2.2.2.1 *Patient and study characteristics*

A total of 14 studies were included in the primary aim. With the exception of three qualitative studies (Miller, Karpinski, & Jezewski, 2012; Miller & Jezewski, 2006; Miller, Jezewski, Miller, & Jezewski, 2001), the studies mostly consisted of surveys and questionnaires. Data from some studies was derived from baseline measures of randomised-controlled trials (Zimmer et al., 2015; Köpke et al., 2014; Mohr et al., 1996). Two quantitative studies were found to have the strongest quality rating (Köpke et al., 2014; Mohr et al., 1996; see appendix 1 for table of results).

Across the 14 studies, a total 8032 patients were included with a range of MS disease subtypes, which comprised: 27 (0.3%) patients with Clinically Isolated Syndrome (CIS), 2,532 (31.5%) Relapsing-remitting MS (RRMS) patients, 349 (4.3%) Primary

Progressive MS (PPMS) patients and 870 (10.8%) Secondary Progressive MS (SPMS) patients. Of the remaining, 251(3.1%) patients were reported as having benign MS, with unclear or unreported MS disease subtype for all other MS patients (49.8%). The mean age of patients was 42 (range: 34 – 50). The mean value excludes MS patients in studies that only stated the median values of age (Visser & Van Der Zande, 2011), the range of ages (Miller & Jezewski, 2006; Miller et al., 2001) and those studies that did not specify age of MS patients (Mohr et al., 1996; Vlahiotis et al., 2010).

Of the studies which recorded the patient's current DMD, the majority of patients were taking first-line treatments, including interferons in seven studies (Abolfazli et al., 2014; de Seze, Borgel, & Brudon, 2012; Köpke et al., 2014; Miller et al., 2001; Mohr et al., 1996; Syed, Rog, Parkes, & Shepherd, 2014; Vlahiotis et al., 2010) and glatiramer acetate in four studies (de Seze et al., 2012; Köpke et al., 2014; Miller & Jezewski, 2006; Vlahiotis et al., 2010). MS patients taking aggressive medications were also recorded, including natalizumab (Miller et al., 2012), fingolimod (Zimmer et al., 2015) and mitoxantrone (Hofmann et al., 2012; Vlahiotis et al., 2010). Eight studies focused primarily on MS patients taking a single DMD (Zimmer et al., 2015; Abolfazli et al., 2014; Hofmann et al., 2012; Miller et al., 2012; Miller & Jezewski, 2006; Miller et al., 2001; Mohr et al., 1996; Syed et al., 2014; see section 1.2 for reviews about DMDs).

2.2.2.2 *Study outcomes*

Understanding of overall treatment information

MS patients' understanding of overall DMD information during their routine healthcare system was assessed using questionnaires and surveys by seven studies.

Self-report measures in one study indicated that 44% of MS patients considered themselves extremely well-informed about their current DMD (Syed et al., 2014). Using a visual analogue scale in another study, just under 20% of patients reported being fully informed about current DMDs (Zimmer et al., 2015). Using retrospective surveys, 28% of

patients reported being well-informed about DMDs at time of diagnosis, with just over 50% patients stating that they did not receive any information about DMDs at diagnosis (Heesen, Kolbeck, Gold, Schulz, & Schulz, 2003). On the other hand, between 75% to 84% of MS patients reported being partly or totally informed about current DMDs (de Seze et al., 2012; Visser & Van Der Zande, 2011), and 85% of MS patients felt they were aware about other DMD treatment options based on one question from a 12-item questionnaire (Vlahiotis et al., 2010). Of those patients who felt informed about DMDs, 71% of MS patients felt the information received was of a sufficient standard (Heesen et al., 2003).

Objective measurements were used by two studies within the present review to establish MS patients' understanding of overall treatment information. Abolfazli and colleagues (2014) administered a 25-item questionnaire to MS patients, nine questions of which assessed understanding of the first-line treatments in general, and three questions each focused on understanding of the five specific DMDs that fell within this category. Only 30% of MS patients were able to correctly answer seven of the nine questions that assessed understanding of the drugs generally, with the remaining two questions answered correctly by just over 60% of MS patients. The authors concluded that understanding of overall information about first-line DMDs was low for the assessed MS patients (Abolfazli et al., 2014). Another study also employed an objective questionnaire, which was presented to patients as part of a baseline measure before intervention (Zimmer et al., 2015). MS patients in this study answered a median of six questions correctly about overall understanding of their current DMD from a maximum score of 18 (Zimmer et al., 2015). Both studies also analysed factors which were associated with greater understanding by MS patients for overall information about DMDs. A common significant patient factor associated with better understanding across both studies was gender, since females displayed greater understanding of overall information about first-

line DMDs (Abolfazli et al., 2014) and the more aggressive treatment fingolimod (Zimmer et al., 2015). Greater understanding of overall DMD information was also related to: a high level of education (Abolfazli et al., 2014), the delay between onset of symptoms and diagnosis of MS (Abolfazli et al., 2014), increased mobility (Abolfazli et al., 2014), younger age (Abolfazli et al., 2014), ability to self-inject for some first-line treatments (Abolfazli et al., 2014) and patients who were in a relationship as opposed to being single (Zimmer et al., 2015).

In summary, the majority of studies which assessed MS patients' understanding of overall DMD information relied heavily on patient self-reports. Although the findings varied both within and across studies, it is clear that not all patients feel sufficiently informed about DMDs during the routine healthcare system. This is also supported by objective measures, albeit in only a few studies. The factors associated with good understanding of overall DMD information were also inconsistent, with only females showing a consistent advantage across two studies.

Understanding of treatment risks

MS patients' understanding of treatment risks was evaluated by four studies in this review.

Perceived accurate understanding of the risks of unspecified DMDs was reported by 63% of MS patients in one study (Heesen et al., 2004). A qualitative study interviewing MS patients taking the aggressive treatment natalizumab showed mixed findings for understanding of the risks associated with this treatment; patients demonstrated both high and low perceived risk (Miller et al., 2012).

Three studies used objective questionnaires to assess understanding of DMD risks, with two of these studies administering a similar adapted 19-item questionnaire designed for newly diagnosed patients (Heesen et al., 2004; Köpke et al., 2014).

Approximately 30% of MS patients showed ‘good risk knowledge’ for their DMD based on their scores from this questionnaire (Köpke et al., 2014). For the other study employing a similar questionnaire, MS patients were only able to answer 34% of the questions correctly on average despite perceiving their risk knowledge as good (Heesen et al., 2004). Significant correlations were also established between greater understanding of DMD risks and patients who had been recently diagnosed, had the RRMS disease subtype, and were of a younger age (Heesen et al., 2004). To note, questionnaires employed in both studies primarily measured understanding of the risks associated with MS in general, with only a portion of the questions explicitly focusing on risk understanding of DMDs. In another study employing objective methodology for the understanding of the aggressive DMD mitoxantrone, 55% of MS patients underestimated the risk of leukaemia, and up to 82% of MS patients underestimated the risk of cardiotoxicity; both adverse risks associated with this DMD (Hofmann et al., 2012). These findings were based on baseline measures of an interventional study (Hofmann et al., 2012).

In summary, although MS patients show mixed perception towards their understanding of DMD risks, objective measures seem to indicate that DMD risks are generally low and underestimated by MS patients during the routine healthcare system.

Understanding of treatment benefits

MS patients’ understanding of the benefits associated with their treatment was evaluated by five studies in the present review.

Over 70% of MS patients taking a range of DMDs believed their current DMD could help their MS (Vlahiotis et al., 2010). Likewise, a large number of MS patients totally or partially perceived their current medication to have strong benefits: 90% of MS patients perceived that their DMD could reduce the frequency of MS relapses, 86% of MS patients believed that their current medication could delay the progression of disease

and just over 70% of MS patients were generally optimistic about their condition as a result of taking their current medication (de Seze et al., 2012). In two qualitative studies, MS patients taking first-line treatments described their medication as a “saviour” (Miller et al., 2001) and believed that taking the DMD felt as if they were “doing something progressive” towards their condition (Miller & Jezewski, 2006).

Only one early study employed an objective methodology to measure understanding of DMD benefits. Mohr and colleagues (1996) administered a 12-item questionnaire prior to providing an intervention. Only 39% of MS patients accurately reported the benefits of taking their first-line DMD, and 57% of MS patients were found to optimistically and incorrectly state that MS relapses could be reduced by a half following uptake of their current DMD (Mohr et al., 1996).

Acknowledging the difficulty of comparing studies with self-report and objective measures, and those encompassing MS patients taking a range of DMDs, the limited data in the current review indicates a general trend towards underestimation of treatment risks and overestimation of treatment benefits by MS patients during the routine healthcare system.

2.2.3 Results of secondary aim

2.2.3.1 Patient and study characteristics

The studies in this part of the review consisted mostly of surveys and questionnaires. One study that has previously been reviewed in the primary aim also included findings relevant to the secondary aim (Abolfazli et al., 2014). Only one study in this section of the review was found to have the strongest quality rating (Kasper, Köpke, Mühlhauser, Nübling, & Heesen, 2008; see appendix 1 for table of results).

From the final 9 studies included into the secondary aim, a total of 7427 patients were included with a range of MS disease subtypes, comprising of: 45 (0.6%) CIS

patients, 652 (8.4%) RRMS patients, 31 (0.4%) PPMS patients and 59 (0.8%) SPMS patients. Majority of the studies did not clearly report or specify the MS disease subtype (89.8%). The mean age of MS patients was 42 (range: 34 – 52).

Of the studies which reported the current DMDs of MS patients, the majority reported patients taking first-line treatments, which includes interferons in five studies (Abolfazli et al., 2014; Prosser et al., 2002; Tur et al., 2013; Wilson et al., 2014; Wilson et al., 2015) and glatiramer acetate in four studies (Prosser et al., 2002; Tur et al., 2013; Wilson et al., 2014; Wilson et al., 2015). Patients taking more aggressive DMDs also formed a part of this review, specifically patients taking natalizumab (Johnson et al., 2009; Tur et al., 2013; Wilson et al., 2014; Wilson et al., 2015), fingolimod (Wilson et al., 2014; Wilson et al., 2015) and rituximab (Wilson et al., 2015). Two studies focused primarily on a single DMD (Abolfazli et al., 2014; Johnson et al., 2009).

2.2.3.2 Study outcomes

Preferences for treatment risks

Four studies, each employing objective methodologies, looked at MS patients' preferences for the risks of taking a treatment.

Tur and colleagues (2013) assessed the level of risks that MS patients were willing to accept for hypothetical therapeutic scenarios. The authors also assessed the relationship between accepted levels of hypothetical treatment risks and current DMDs taken by MS patients. A visual analogue scale showed that MS patients on the aggressive treatment natalizumab were willing to accept higher levels of hypothetical treatment risks in comparison to MS patients on any other DMD (Tur et al., 2013).

Hypothetical treatment scenarios were employed by two further studies using objective methodologies, which compared MS patients' preferences for different levels of treatment risks (Wilson et al., 2014; Wilson et al., 2015). Both studies confirmed that

DMDs with significant adverse risks were less preferred than DMDs with minor side-effects. In fact, both studies revealed that medications with no possibility of death or disability were significantly favoured to a medication with even a very low possibility (0.05% to 1%) of death or disability (Wilson et al., 2014; Wilson et al., 2015). Mood changes were the only side-effect that would decrease the probability of taking a DMD by MS patients (Wilson et al., 2014; Wilson et al., 2015).

Using a standard gamble question task, another study employed a hypothetical treatment scenario which presented information about a treatment that could cure MS, and a real treatment scenario which presented the risk profile of the aggressive DMD natalizumab (Fox et al., 2015). MS patients showed similar preferences for risks in both the hypothetical and real treatment risk scenarios, as adverse risks were accepted when in the range of 1 in 10,000 (Fox et al., 2015). For the hypothetical treatment scenario, MS patients that were significantly likely to prefer higher levels of adverse risks were those presenting with the following characteristics: wheelchair bound, male, not responsible for dependents, not currently taking a DMD, taking natalizumab and not routinely wearing a seatbelt for car travel (Fox et al., 2015). With the exception of MS patients who were not taking a DMD, the same characteristics of MS patients preferred higher levels of treatment risks in the real DMD scenario (Fox et al., 2015).

Despite the comparison of hypothetical and real treatment risk profiles in this section of the review, MS patients showed similar low preferences for treatment risks.

Preferences for treatment benefits

MS patients' preferences for treatment benefits were assessed by five studies in the present review.

Two studies used subjective measures to assess the preferences of MS patients towards treatment benefits (Abolfazli et al., 2014; Kasper et al., 2008). The number of

MS patients with a positive outlook towards their current DMD ranged from 20% to 90% within one study (Abolfazli et al., 2014) and was approximately averaged at 60% in another (Kasper et al., 2008). Patient factors significantly associated with a positive attitude were patients with: lack of functional problem, no MS family history and knowledge of their current DMDs (Abolfazli et al., 2014).

Turning to objective measures, Prosser and colleagues (2002) utilised a gamble health outcomes task using hypothetical treatment scenarios to assess preferences of MS patients for treatment benefits. During this task, patients were required to choose either a drug offering a particular number of relapse-free days, or a drug offering a 50% chance of ending the MS relapse immediately but with 50% chance of the drug not working at all. On average, patients chose drugs likely to lead to 14.6 MS relapse-free days from the possible 29, implying a preference towards treatments offering moderate but guaranteed benefits. However, the authors did note that approximately 30% of MS patients chose an extreme number of relapse-free days, i.e. either 1 or 29 (Prosser et al., 2002).

The frequency of MS relapses was also used as an outcome measure to assess MS patients' preferences for treatment benefits in the remaining two studies and was compared alongside other benefits that DMDs typically offer (Wilson et al., 2014; Wilson et al., 2015). The highest preference for MS patients in one study was for substantial symptom improvement in MS, followed by prevention of disease progression over 10 years, mild symptom improvement and a five-year delay in MS relapses (Wilson et al., 2014). Administration in the form of an IV infusion or oral pill was also significantly preferred by MS patients. In fact, the ability to administer the drug orally was preferred even over a five-year delay in relapse (Wilson et al., 2014). Likewise, any form of improvement in symptoms and the ability to take the drug orally were also strongly preferred by MS patients in the latter study (Wilson et al., 2015). However, unlike the previous findings, MS patients in this study showed no significant preference for delay in

MS relapses or administration of drugs via IV infusion (Wilson et al., 2015). Additionally, the ability to prevent MRI progression over the years was used as an indicator only in this study and was significantly preferred by MS patients (Wilson et al., 2015).

Although all studies in this review assess MS patients' preferences for treatment benefits, chiefly for hypothetical treatment scenarios, the results are not directly equivalent as the range and actual treatment benefits offered to patients differed greatly between studies. In general, treatments offering high symptom improvement, a delay in disease progression, reduction in relapses and particular administration methods were preferred.

Preferences for treatment risk-benefit profiles

Three studies objectively measured the risk-benefit trade-off by offering MS patients the choice of benefits and risks for hypothetical treatments, using the conjoint analysis method (Johnson et al., 2009; Wilson et al., 2014; Wilson et al., 2015). Whilst all three studies used a similar objective methodology, the studies employed different treatment risk and benefit scenarios. Johnson and colleagues (2009) demonstrated that for a five-year delay of disease progression, a 0.48% risk of death by Leukaemia was acceptable for MS patients; which increased to 1.08% for an eight-year delay of disease progression. For a similar delay of disease progression, the acceptable risk of death by liver failure increased by 0.53%, and acceptable risk of severe disability or death from PML increased by 0.36% (Johnson et al., 2009). Wilson and colleagues (2014) found that patients were willing to accept 0.7% risk of developing PML given a delay in the progression of disease. Up to 1% adverse risks were accepted by MS patients if substantial improvements in symptoms could be demonstrated by the treatment (Wilson et al., 2014). Patients were willing to accept up to 0.59% of severe adverse effects if drugs could be administered orally (Wilson et al., 2014). In fact, this level of risk

acceptance was higher than for drugs which could delay the progression of MS by four years (Wilson et al., 2014) or could reduce the frequency of MS relapses from four yearly to no relapses within the next five years (Johnson et al., 2009). Further, a risk of up to 30% of severe adverse effects was acceptable for MS patients given 32 years of delay in progression of MS (Wilson et al., 2015).

The study by Bruce and colleagues (2015) also assessed risk and benefit trade-offs of hypothetical treatment scenarios by using a Medical Decision Making Questionnaire (MDMQ). Similar to previous studies, the choice of whether to uptake a treatment for all patients differed significantly according to the combination of treatment risks and benefits (Bruce et al., 2015). Additionally, patients who were adherent to their current unspecified treatment were willing to take medications with significantly higher combinations of risks and benefits than patients who were identified as non-adherent (Bruce et al., 2015).

In summary, despite using similar measures to objectively assess trade-offs of treatment risks and benefits, the three studies employed very different combinations of risks and benefits, limiting any generalised conclusions that may be based on these findings. However, it was clear from these studies that preferred combinations of treatment risks and benefits play a key role in the choice of treatment.

2.2.4 Discussion

This systematic review was conducted to explore MS patients' understanding of DMD risks and benefits acquired through standard healthcare and MS patients' preferences for these risks and benefits; factors likely to impact shared decision-making. MS patients with different disease subtypes and those taking a range of DMDs were assessed by 22 studies in the present review. Understanding of DMD risks and benefits were mostly addressed as part of a larger project. MS patients' preferences for risks and benefits were generally assessed using treatments offering hypothetical risks and benefits.

Studies employed both subjective and objective measures. The majority of studies had methodologies that precluded firm conclusions.

For effective decision-making, clear and accurate DMD information should be provided to MS patients in order to facilitate understanding of treatment risks and benefits. Yet, it appears from the present review that MS patients do not sufficiently understand information about DMDs following routine consultations in their standard healthcare system. Despite evaluating their risk knowledge as high (Heesen et al., 2004), MS patients in this review showed poor objective risk understanding (Heesen et al., 2004; Köpke et al., 2014). There was a trend towards underestimation of treatment risks (Hofmann et al., 2012; Vlahiotis et al., 2010). This is problematic for long-term treatment adherence as some patients are likely to initiate a treatment that they perceive has lower risks but then discontinue treatment when the risks are higher than initially expected (Colombo et al., 2014; Lizan et al., 2014). MS patients in this review were generally optimistic about the benefits of their current DMD (Kasper et al., 2008; Miller et al., 2012; Miller et al., 2001; Vlahiotis et al., 2010). However, many patients overestimated the benefits of their DMD in reducing the frequency of relapses and delaying progression of disease (de Seze et al., 2012; Mohr et al., 1996). Thus, patients' optimism towards DMDs may not often accurately reflect the actual benefits of the drugs. This can further impact treatment adherence since patients who do not accurately understand the benefits of DMDs are more likely to discontinue treatments over time (Lizan et al., 2014), perhaps as optimism for medications is replaced with the realisation that the medication does not offer expected levels of benefits. In fact, a significant relationship between patients who understand information about their treatments and their adherence to treatments is apparent in several studies, including those in the present review (de Seze et al., 2012; Köpke et al., 2014; Lizan et al., 2014; Twork et al., 2007). Providing accurate and easily

understandable risk and benefit information to MS patients should therefore improve treatment adherence towards their chosen treatment.

Effective shared decision-making also requires patients to communicate their preference for a particular treatment. Preferences for risks and benefits of treatments are likely to influence decisions about which treatment to initiate (Currie et al., 2014; Fraenkel, 2013; Gong et al., 2015). The secondary aim of the present review therefore assessed the extent to which preferences towards risks and benefits that DMDs typically offer can impact MS patients' treatment decisions. As anticipated, even very low levels of adverse risks reduced patients' preference to take the treatment, and extremely small variations in risk had a significant impact on hypothetical treatment decisions (Fox et al., 2015; Wilson et al., 2014; Wilson et al., 2015). Preference for medications with adverse risks rarely exceeded 1%. Preferences for risks also varied with certain patient factors, as higher risks were generally accepted by males, functionally impaired individuals, or people already taking aggressive treatments such as natalizumab (Fox et al., 2015; Tur et al., 2013). Similarly, certain benefits that DMDs typically offer were significantly preferred over others and had an impact on the choice of treatment. Remarkably, patients strongly favoured medications that could provide symptom improvement (Wilson et al., 2014; Wilson et al., 2015), which implies limited understanding of MS treatments since DMDs are not able to relieve symptoms of MS. Note, however, that medications presented in both studies employed hypothetical treatment scenarios and therefore it is possible that patients perceived symptom improvement as hypothetical despite accurate understanding of DMD benefits (Wilson et al., 2014; Wilson et al., 2015). It is nevertheless interesting that patients are likely to take higher risks if DMDs can seemingly help improve symptoms of their condition. MS patients in this review also showed a greater preference for treatments offering large reductions in frequencies of relapses, longer delay in disease progression and drugs that could be administered orally,

being prepared to accept a greater likelihood of risk in return (Bruce et al., 2015; Johnson et al., 2009; Wilson et al., 2014; Wilson et al., 2015).

Overall, MS patient preferences varied according to different combinations of treatment risks and benefits, and had a significant impact on their choice of treatment. Thus, it is important to elicit patient preferences for DMD risks and benefits alongside increasing patients' understanding of treatments, in order to improve shared decision-making in MS.

2.3 Systematic review 2: Interventions to support MS patients' understanding of DMDs²

The first systematic review showed that MS patients do not have sufficient understanding of the complex risk-benefit profiles of DMDs. To facilitate understanding, patients should ideally be presented with treatment options and treatment risk-benefit profiles in a clear and coherent manner (Bunge et al., 2010; Thompson, 2013). Interventions have been designed to provide information about the risks and benefits of DMDs that patients may seek beyond routine healthcare. Köpke, Solari, Khan, Heesen and Giordano (2014) recently reviewed 10 interventions designed to aid patient understanding of MS related information, which includes two interventions that specifically provided information about the risks and benefits of DMDs. Although all interventions reviewed were different in many respects, understanding of the disease generally improved post-intervention. Despite this improvement there was no conclusive effect on decision-making. This review, however, was limited to randomised controlled trials only, which does not allow for a comprehensive evaluation of all interventions that provide MS information beyond routine healthcare, particularly information on the risks and benefits of DMDs (Köpke et al., 2014).

² This systematic review has been published as: Reen, G. K., Silber, E., & Langdon, D. W. (2016). Interventions to support risk and benefit understanding of disease-modifying drugs in Multiple Sclerosis patients: A systematic review. *Patient Education and Counseling*. (see appendix 2).

Thus, a second systematic review was conducted to evaluate interventions that have been primarily designed to improve understanding of risks and benefits of DMDs for MS patients.

2.3.1 Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were used as guidelines for the presentation of this review (Moher, Liberati, Tetzlaff, Altman, & Grp, 2009).

2.3.1.1 Systematic literature search

The systematic literature search was also conducted in April 2015 and updated for publication in November 2016. The search was carried out using PubMed, Embase, Google Scholar and PsycINFO. Uniform search terms were developed and used with all databases (see table 2.2).

Table 2.2 Search terms for systematic review 2

Search terms
(Multiple AND Sclerosis)
AND
(patients OR people OR persons OR patient)
AND
(risk OR benefit OR side effect OR treatment OR medication OR therapy OR medicine OR medical OR therapies OR therapeutics OR pharmaceutical preparations)
AND
(format OR framing OR educating OR design OR informing OR health literacy OR strategy OR program OR intervention OR communicating OR information OR education OR learning)
AND
(perception OR understanding OR comprehension OR awareness OR knowledge OR decision-making)

2.3.1.2 Eligibility criteria

The inclusion criteria for the studies in the present review were studies in English, with human adults and with patients of any clinical subtype of MS. No date restriction was applied. Studies were not limited to any particular study design. No restrictions were placed on the type of control group. Studies were required to have interventions which provided information about treatments to MS patients. These interventions could either include real DMD information or information about fictitious treatments which would eventually support the understanding of DMD information. The studies were excluded if they consisted of information about complementary medicines or medications for the management of MS symptoms. Interventions were defined as any additional strategy or decision-aid which provided treatment information beyond that given during routine healthcare. Studies with some form of evaluation of these interventions were retained.

Studies were excluded if they evaluated educational interventions for complementary medicines or medications for the management of MS symptoms. Studies assessing patients' understanding of disease diagnosis or prognosis were not eligible for inclusion. Studies without any form of educational intervention, with interventions based on other aspects of MS such as cognition or self-management, interventions aimed primarily at health professionals, an intervention protocol for an upcoming study with no existing data, or interventions not exclusive to patients with MS, were also excluded from the review.

All titles and abstracts were screened. Studies that were considered relevant from additional reference checking were also included. At this stage, 96 studies were considered for eligibility and full texts were subsequently accessed (see figure 2.2).

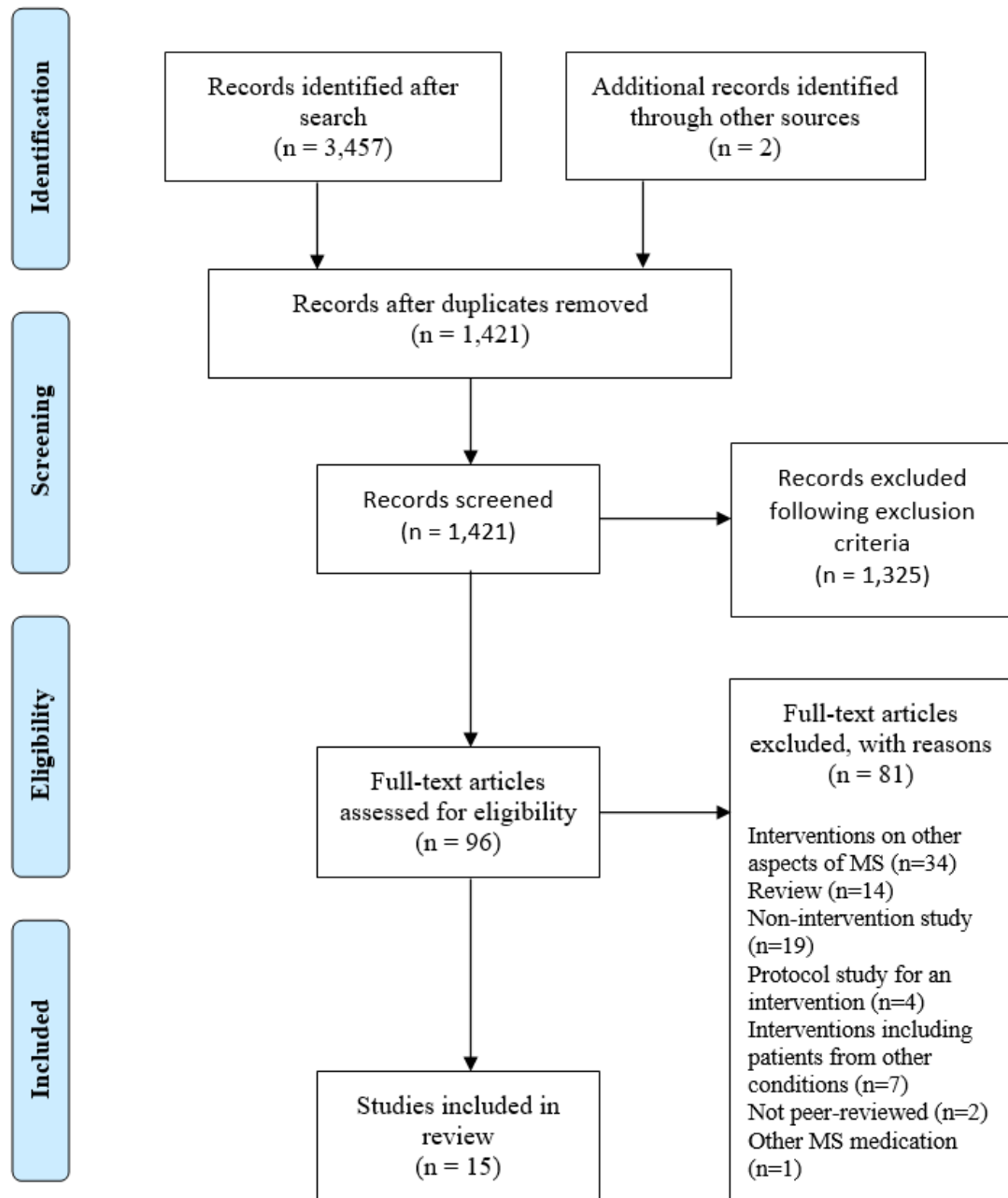


Figure 2.2 PRISMA flow chart for studies included in systematic review 2

2.3.1.3 Data extraction

Data extraction forms were created to extract relevant information from the full texts, and assess their eligibility into the final review. Extraction was initially carried out by one reviewer (GR) and was verified by another (DL). Any discrepancies were

resolved by discussion. Following data extraction, 81 studies were excluded from the final review (see figure 1).

Baseline characteristics of participants were extracted from the 15 shortlisted studies, comprising (where reported) age, type of MS, disease duration, time since diagnosis and current DMD. Study design and methodology was recorded. Information about the interventions was further extracted, including the content, length, presentation methods and any additional details of how the interventions were conducted.

The impact of the interventions on either understanding of treatment information overall or understanding of treatment risks and benefits specifically was also extracted in the present review and incorporates data from self-report and objective measures. Patients' feedback of the interventions was also retained. Relevant data for the present review was obtained from numerical information in texts, tables and graphs, and statistical analysis.

2.3.1.4 Quality assessment

Quality was independently examined by two reviewers (GR and DL) using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies (Thomas et al., 2004). This particular tool was chosen as it can evaluate all types of quantitative studies in the health care setting (Armijo-Olivo et al., 2012), has high inter-rater reliability (Armijo-Olivo et al., 2012) and is often considered ideal for systematic reviews (Deeks et al., 2003). As per the tool, the final quality rating was derived from the rating of six measures: selection bias, study design, confounders, blinding, data collection methods, and withdrawals or drop-outs.

2.3.2 Results

2.3.2.1 Study design and participant demographics

Fifteen studies were shortlisted in the review and comprised interventions which were primarily designed to improve understanding of DMD risk and benefit information in MS patients. Four studies in this review evaluated interventions using a randomised controlled procedure (Kasper et al., 2008; Kasper, Heesen, Köpke, Mühlhauser, & Lenz, 2011; Köpke et al., 2014; Rahn et al., 2016). A type of control group was present in seven studies (Basso et al., 2010; Feicke, Spörhase, Köhler, Busch, & Wirtz, 2014; Heesen et al., 2010; Kasper et al., 2008; Köpke et al., 2016; Köpke et al., 2014; Rahn et al., 2016) and baseline scores prior to the intervention were recorded by ten studies (Zimmer et al., 2015; Feicke et al., 2014; Freidel, Ortler, Fuchs, Seibert, & Schuh, 2015; Hofmann et al., 2012; Kasper et al., 2011; Kasper, Köpke, Mühlhauser, & Heesen, 2006; Köpke et al., 2016; Köpke et al., 2014; Mohr et al., 1996; see appendix 2 for table of results).

Five of the 15 studies were considered to be of a high quality (Kasper et al., 2008; Kasper et al., 2011; Köpke et al., 2016; Köpke et al., 2014; Mohr et al., 1996), with three studies deemed weaker in quality (Colombo et al., 2016; Hofmann et al., 2012; Rahn et al., 2016). Four of the 15 studies had interventions that fulfilled or reported at least 4 of the 8 criteria for evidence-based patient information. The most commonly reported criteria in the interventions were the use of comprehension enhancing tools, involvement of patients in the development process and inclusion of numerical data.

A total of 2552 MS patients were included across 15 studies and had a range of MS disease subtypes, comprising: 79(3.1%) CIS patients, 1064 (41.7%) RRMS patients, 214 (8.4%) PPMS patients and 391 (15.3%) SPMS patients. The remaining MS patients had unclear or unreported MS disease subtype (31.5%). The mean age of patients was 43.1 years (range: 37– 50). One study did not allow for calculation of mean age (Mohr et

al., 1996) and two studies only presented median or mode values for age (Zimmer et al., 2015; Heesen et al., 2010). Two studies also included 105 non-MS patients with a mean age of 43.5 years (Basso et al., 2010; Colombo et al., 2016).

Nine studies reported patients' disease duration from initial MS symptoms (Colombo et al., 2016; Feicke et al., 2014; Heesen et al., 2010; Hofmann et al., 2012; Kasper et al., 2011, 2006; Köpke et al., 2014; Rahn et al., 2016; Tur et al., 2012), with an average of 9.2 years. Five studies reported time since MS diagnosis (Zimmer et al., 2015; Freidel et al., 2015; Kasper et al., 2008; Köpke et al., 2016; Köpke et al., 2014), with an average of 5.8 years.

Only one included study reported patients' objective cognitive status (Basso et al., 2010). Patients were assessed on the California Verbal Learning Test-II (CVLT-II), Wisconsin Card Sorting Test-64 (WCST) and the Digit Span subtest from Wechsler Adult Intelligence Scale. MS patients were considered to be cognitively impaired if they scored below the 5th percentile of at least one cognitive measure (Basso et al., 2010).

A total of 1384 (54.2%) MS patients had taken disease-modifying drugs during the course of their disease and 188 (7.4%) MS patients had not taken a DMD. The remaining studies did not specify DMD status (980 MS patients, (38.4%)). Of studies reporting MS patients' current DMD, 273 patients were on the first-line treatment interferon-beta (Freidel et al., 2015; Köpke et al., 2014; Mohr et al., 1996), and the remaining patients were taking second-line treatments, with 53 patients on Mitoxantrone (Hofmann et al., 2012), 173 patients on Natalizumab (Heesen et al., 2010; Tur et al., 2012) and 98 patients on fingolimod (Zimmer et al., 2015). In majority of these studies, DMD status was known by treating physicians or researchers involved with the study (Zimmer et al., 2015; Feicke et al., 2014; Freidel et al., 2015; Heesen et al., 2010; Hofmann et al., 2012; Mohr et al., 1996; Tur et al., 2012).

2.3.2.2 *Intervention characteristics*

Intervention type

The majority of interventions contained a booklet or leaflet for MS patients (Freidel et al., 2015; Heesen et al., 2010; Hofmann et al., 2012; Kasper et al., 2008; Kasper et al., 2011; Köpke et al., 2014; Tur et al., 2012). These leaflets ranged from providing comprehensive information (120 pages, (Kasper et al., 2008); 57 pages (Köpke et al., 2014)) to short summaries (Heesen et al., 2010; Hofmann et al., 2012). The booklet length was unclear in three studies (Freidel et al., 2015; Kasper et al., 2008; Tur et al., 2012). Three interventions which included booklets also contained an additional intervention component (Freidel et al., 2015; Kasper et al., 2008; Köpke et al., 2014). A short vignette of information was read aloud in one intervention but was not handed to patients in the form of a booklet or leaflet (Basso et al., 2010).

Four studies evaluated interventions with interactive modules, defined as involving patients during the intervention process. This includes discussions (Zimmer et al., 2015; Köpke et al., 2014), exercises (Kasper et al., 2008; Köpke et al., 2014) and questions and answers (Freidel et al., 2015; Köpke et al., 2014).

Multicomponent educational programmes were utilised as an intervention in four studies. Four of these programmes were conducted by health professionals (Zimmer et al., 2015; Freidel et al., 2015; Köpke et al., 2016; Mohr et al., 1996) and one education programme was conducted by a non-medical person (Köpke et al., 2014).

Intervention content

All but one intervention (Mohr et al., 1996), provided some form of treatment risk information to patients with MS. Interventions also included information about: treatment benefits (Basso et al., 2010; Kasper et al., 2008; Kasper et al., 2011; Köpke et al., 2014; Mohr et al., 1996), alternative DMDs available to patients (Basso et al., 2010;

Köpke et al., 2014), efficacy studies for DMDs (Zimmer et al., 2015; Köpke et al., 2014), DMD decision-making (Kasper et al., 2008; Köpke et al., 2014), administration of DMDs (Zimmer et al., 2015; Freidel et al., 2015) and tailored information about DMDs for patients' disease subtype (Kasper et al., 2008; Tur et al., 2012).

Intervention presentation methods

Many different methods to present information were employed in the interventions. Methods which provided numerical information was manipulated by some studies, for instance by presenting or giving explanations for absolute risk numbers (Hofmann et al., 2012; Kasper et al., 2008; Kasper et al., 2011) and relative risk numbers (Kasper et al., 2011). Two studies used graphical formats in the form of pictograms to give treatment information (Kasper et al., 2008; Kasper et al., 2011). One study focused on whether the information was framed in a positive or negative manner (Kasper et al., 2008).

Some interventions also provided treatment information using interactive methods, which includes: questions and answers (Freidel et al., 2015; Köpke et al., 2014), discussions in person (Freidel et al., 2015; Köpke et al., 2014), recognition cues (Basso et al., 2010), information presented in short successions (Basso et al., 2010) and interactive exercises presented at the end of interventions (Zimmer et al., 2015; Kasper et al., 2008; Köpke et al., 2014). Media and technology was used to present treatment information in two studies (Köpke et al., 2014; Mohr et al., 1996).

Together, these strategies were designed to optimise understanding of the risks and benefits of DMDs.

2.3.2.3 *Intervention outcomes*

Understanding of overall treatment information.

Two studies looked at understanding of overall treatment information with no particular focus on the risks or benefits of treatments. Both employed an objective comprehension questionnaire to assess understanding, but maximum scores ranged from 6 to 18.

Despite no significant difference in the understanding of treatment information between a non-clinical control group and MS patients without cognitive impairment, both groups were significantly better than cognitively impaired MS patients (Basso et al., 2010). The control and MS cognitively unimpaired group showed greater understanding following information provided in short successions or when recognition cues were provided to aid recall of information, compared to when treatment information was provided in an uninterrupted block (Basso et al., 2010). A similar trend was observed in the cognitively impaired MS group. However, this group also showed a significant improvement in understanding when recognition cues were given alongside treatment information provided in short successive steps, in comparison to information provided in successive steps alone (Basso et al., 2010). In two other studies, a significant increase in understanding of overall treatment information was also evident following intervention when compared to both baseline understanding (Zimmer et al., 2015) and a control group receiving standard information (Rahn et al., 2016). However, there was no significant improvement on patients' understanding post-intervention when the control group received identical content as the intervention in a non-interactive form (Feicke et al., 2014).

To note, studies differed in the content of the intervention, as only two of the four studies provided information about real DMDs (Zimmer et al., 2015; Feicke et al., 2014).

Further, only some items in the questionnaires used to assess patients' understanding focused specifically on treatment-related information.

In summary, although there is a trend towards an improvement in understanding of overall treatment information following intervention, this cannot be established with just two studies employing different interventions and comparison groups.

Treatment risk understanding.

The understanding of treatment risks in MS patients following intervention was assessed objectively by three studies, using real DMD information in two studies (Hofmann et al., 2012; Köpke et al., 2014) and a hypothetical treatment information in another (Kasper et al., 2011).

Following a short leaflet about risks of taking Mitoxantrone, MS patients showed a significant increase in accurate risk understanding of leukaemia, an adverse risk associated with the medication (Hofmann et al., 2012). This risk was initially underestimated by 58% of MS patients (Hofmann et al., 2012). Underestimation of risk persisted in 18% of MS patients following intervention. Improved risk understanding was not dependent on demographic factors, disease duration or the available scientific evidence at treatment initiation. However, patients with large errors on the Medical Data Interpretation Test (MDIT), which assessed the ability to handle probability data, showed an underestimation of Leukaemia risk after reading the leaflet (Hofmann et al., 2012). Following an intervention with a 4-hour education programme combined with a 57-page leaflet, understanding of the first-line DMD risks significantly improved for patients in the intervention group compared to MS patients in the control group (Köpke et al., 2014). Similar results were seen with another multi-component intervention, consisting of a 2-hour and 4-hour education programme, in addition to a 120-page information brochure (Köpke et al., 2016). In comparison to the control group receiving standard information brochure and a rehabilitation programme, the intervention group showed a significant

increase in DMD risk understanding at 2 weeks and 6 months post-intervention (Köpke et al., 2016).

One study measured risk understanding using self-report questions after trialling a DMD informational website for interferons (Colombo et al., 2016). Over 80% of MS patients stated that they found the presented risk information really or extremely clear and easy to understand (Colombo et al., 2016).

Using hypothetical treatment information, Kasper and colleagues (2011) showed that the ability to recall treatment risks from pictograms to frequencies was generally low. However the authors noted that risks were recalled more accurately than benefits (Kasper et al., 2011). Mean errors in recalling risks from pictograms which displayed figures consecutively were significantly lower as opposed to pictographs with random arrangement of figures (Kasper et al., 2011). Patients that attributed high personal risk of becoming wheelchair dependent within two years showed a small correlation with overestimation of risk following intervention (Kasper et al., 2011).

Overall, understanding of treatment risks showed an improvement of reasonable accuracy post-intervention despite the variety of interventions employed across the reviewed studies.

Treatment benefit understanding.

Understanding of treatment benefits was assessed objectively by four studies post-intervention (Heesen et al., 2010; Kasper et al., 2011, 2006; Mohr et al., 1996) and with self-report measures by one study (Colombo et al., 2016).

Following a 3-page information booklet, MS patients showed significant improvements in understanding of interferon benefits post-intervention when compared to baseline (Kasper et al., 2006). The authors did note that around 99 of 169 patients were still not able to understand the information after intervention (Kasper et al., 2006).

Following another educational intervention, there was a significant reduction in patients that were overly optimistic about the general benefits of their DMD, even though overestimation persisted in about 33% of individuals (Mohr et al., 1996). At baseline, approximately 34% of MS patients were unrealistically optimistic about the benefits of their medication on disease progression specifically. Yet post-intervention, the number of MS patients overestimating these specific benefits about their current medication increased to about 40% (Mohr et al., 1996). Likewise, in another study, MS patients believed that their medication will provide a greater reduction of risk for a maximum walking distance of 100m following the short leaflet-based intervention on natalizumab in comparison to physicians (Heesen et al., 2010). Even with hypothetical treatment information, MS patients overestimated the benefits of the fictitious treatment by more than 100% following intervention (Kasper et al., 2011).

Using self-report measures, over 75% reported that the interferon benefits presented in a DMD informational website were really or extremely clear and that graphical presentations of treatment benefits were easy to understand (Colombo et al., 2016).

In summary, initial overestimation of treatment benefits seemingly persists despite interventions that provide treatment benefit information beyond routine healthcare, although many patients report their own understanding of treatment benefits following intervention as high.

Attitude towards treatment risks.

Beyond understanding of treatment risk, two studies also assessed personal perception for treatment risks following interventions that provided information about real DMDs (Heesen et al., 2010; Hofmann et al., 2012).

Following a short leaflet about natalizumab, 84% of MS patients were willing to accept a 1 in 100 or higher risk of PML, an adverse side-effect of the medication, compared to only 51% of physicians; showing a significant difference (Heesen et al., 2010). The authors noted that PML risk acceptance was not correlated with understanding of DMD information (Heesen et al., 2010). Patients' personal risk attribution of PML as an adverse risk of natalizumab was deemed significantly lower than the PML risk they attributed to natalizumab generally post-intervention (Heesen et al., 2010). However, since baseline measures were not recorded in the study, it is difficult to determine whether personal risk attribution changed as a result of the intervention or was previously low at baseline. In another study which did record baseline measures, MS patients showed a significant increase from baseline for both general and personal risk attribution of the adverse risks associated with mitoxantrone after reading the informational booklet (Hofmann et al., 2012). Yet similar to the previous study, personal risk attribution of the adverse risks of the DMD was significantly lower than general attributed risk of adverse risks by the MS patients (Hofmann et al., 2012).

In summary, two studies show that patients attribute lower personal risks of taking their current DMD than general risks they attribute to the DMD, despite improved understanding of their DMD risks post-intervention.

Treatment decisions

Four studies recorded MS patients' decision about their DMD following intervention (Heesen et al., 2010; Kasper et al., 2008; Köpke et al., 2014; Tur et al., 2012).

Using self-report Likert-scales MS patients in the intervention group were found to be significantly more critical about their current DMD compared to baseline and control group, even after four weeks following intervention (Kasper et al., 2008). Likewise, patients were critical towards current DMD after intervention in another study

although this attitude did not persist beyond two weeks (Köpke et al., 2014). In another study, patients reported feeling confident in their decision to choose interferons after receiving information about interferons beyond routine healthcare (Colombo et al., 2016).

MS patients in the intervention group did not show significant differences to the control group in progress of DMD decisions during follow-up in two studies (Kasper et al., 2008; Köpke et al., 2014). When compared with physicians' decisions however, a considerably higher number of patients opted to continue the natalizumab DMD post-intervention (Heesen et al., 2010). Although for the same medication following another intervention, 60% of MS patients discontinued treatment if they had the highest risk of PML, compared to 24% patients with the second-highest PML risk (Tur et al., 2012). No patient discontinued the treatment post-intervention in the lower risk groups (Tur et al., 2012).

In summary, the studies in the present review show a trend towards a critical attitude towards their DMD post-intervention with some discontinuation due to these attitudes, although the impact on patients' decisions was generally inconclusive in the long-term.

Intervention feedback

MS patients in four studies provided feedback on the interventions using self-report measures. Relative to the control group, MS patients in the intervention group felt better informed and felt that important questions had been adequately answered even after six months following intervention (Kasper et al., 2008). Similarly, MS patients deemed the intervention they received as important and felt that this did not increase worries (Hofmann et al., 2012). In fact, 84% of MS patients stated that they would recommend the intervention to other patients (Hofmann et al., 2012). The majority of patients reported the intervention as useful, and were particularly satisfied with specific training they received during the intervention (Freidel et al., 2015). Likewise, there was a

significant increase in patients' perception of being informed, in addition to the feeling of certainty and confidence of being able to handle all treatments following a DMD information intervention (Zimmer et al., 2015). Over 80% of MS patients trialling an informational website reported that the website was easy to navigate, easy to understand and was useful (Colombo et al., 2016). Following informational materials explaining confidence intervals, patients in the intervention group consistently rated the information as being understandable, relevant and beneficial (Rahn et al., 2016).

Despite the diversity of the DMD interventions employed in these four studies, all were positively received which indicates that patients generally perceive any type of interventions as favourable in facilitating understanding of DMD information.

2.3.3 Discussion

This systematic review was conducted to evaluate interventions designed to improve MS patients' ability to understand complex risk-benefit profiles of DMDs. Fifteen studies were reviewed and included MS patients with different clinical subtypes and those taking a variety of DMDs. Studies employed a range of outcome measures and not all studies included baseline data or control group. Some studies had methodologies that precluded firm conclusions.

Interventions within this review provided treatment information using booklets, websites, vignettes and education programmes. Half of the interventions included some form of interactive component (Zimmer et al., 2015; Basso et al., 2010; Feicke et al., 2014; Freidel et al., 2015; Kasper et al., 2008; Kopke et al., 2016; Köpke et al., 2014). There was no apparent advantage of interactive versus passive interventions on understanding. There was also no apparent benefit of longer and multicomponent interventions in comparison to shorter and basic interventions such as leaflets in the current review. From this, it can be presumed that interventions which are easier to administer and require fewer resources may be just as beneficial to employ as longer

interventions. Moreover, less than half of the interventions manipulated or explained the formats used to present treatment information, such as framing, numerical formats or graphical formats (Colombo et al., 2016; Hofmann et al., 2012; Kasper et al., 2008; Kasper et al., 2011, 2006; Rahn et al., 2016). This is surprising considering that presentation formats are a key criteria for an effective evidence-based educational intervention (Bunge et al., 2010) and can significantly impact understanding of treatment information (Berry, Knapp, & Raynor, 2006; Bodemer, Meder, & Gigerenzer, 2014; Hawley et al., 2008; Lipkus, 2007; Price, Cameron, & Butow, 2007). Therefore, the use of presentation formats should be carefully considered when designing an educational intervention.

In general, it was difficult to make comparisons between these interventions since they were very diverse in their content and administration. In particular, it was not possible to draw conclusions about the most effective intervention which could improve understanding of DMD information in MS patients. However studies that recorded patients' feedback of the interventions all received favourable reviews (Zimmer et al., 2015; Colombo et al., 2016; Freidel et al., 2015; Hofmann et al., 2012; Kasper et al., 2008; Rahn et al., 2016), which indicates that any form of intervention providing DMD information beyond routine health-care are generally well-accepted by MS patients in these studies.

In terms of the impact of interventions, four interventions improved understanding of overall information provided during intervention, despite using very different interventions and study designs (Zimmer et al., 2015; Basso et al., 2010; Feicke et al., 2014; Rahn et al., 2016). For treatment risk knowledge specifically, MS patients initially showed an underestimation of treatment risks during routine healthcare, but showed greater understanding of both real and hypothetical treatment risks post-intervention. This improvement in risk understanding seemed related to multicomponent

interventions (Kopke et al., 2016; Köpke et al., 2014), information which was easier to understand (Colombo et al., 2016; Hofmann et al., 2012; Kasper et al., 2011) and when personal risk attribution was perceived as low (Kasper et al., 2011). However, it was not possible to determine the extent to which these interventions were able to improve understanding of both adverse risks and side-effects that are less severe but commonly associated with DMDs. Nevertheless, interventions designed to improve understanding of treatment risks could be very beneficial for patients making treatment decisions, since even very small changes in the risks of DMDs can have a huge impact on treatment choice (Wilson et al., 2014; Wilson et al., 2015). In fact, some studies in the present review showed a trend towards patients becoming critical or discontinuing treatment when risks were better understood (Heesen et al., 2010; Kasper et al., 2008; Kasper et al., 2011; Tur et al., 2012). This suggests that patients are likely to review decisions for their current DMD following new and enhanced understanding of treatment risks. Considering this, it is important that patients perceive information accurately about DMD risks when making initial treatment decisions, so that the true risks associated with their chosen treatment are in line with patients' preferences. Although, some studies in the review showed that despite greater understanding of treatments risks, MS patients seemed to underestimate their personal chance of developing these risks (Heesen et al., 2010; Hofmann et al., 2012). Interventions in the future could therefore attempt to converge personal risk attribution with accurate understanding of treatment risks, to ensure patients are able to apply the knowledge they gain from the intervention and make informed treatment decisions based on personal preferences.

Improvements in understanding the benefits of treatments were less pronounced. Objectively, many patients did not understand or tended to overestimate the benefits of taking their treatment, even after receiving additional information (Heesen et al., 2010; Kasper et al., 2011, 2006; Mohr et al., 1996). This can be problematic for selecting a

course of treatment, as patients are more likely to prematurely discontinue treatment if DMD benefits are perceived as higher than actual benefits (Lizan et al., 2014; Mohr et al., 1996). Such poor adherence to DMDs can have both direct and indirect costs for MS patients (Yermakov et al., 2015). However, patients did not significantly change their treatment decisions following intervention, similar to the review by Köpke and colleagues (2014). It is therefore difficult to determine the effects of accurate understanding of treatment information on treatment adherence and shared treatment decision-making. This affirms that understanding of treatment information is simply a precursor to effective shared decision-making and other key factors such as patient autonomy, patient preferences or decision regret, would also need to be addressed in interventions to directly improve shared treatment decision-making (Barry & Edgman-Levitan, 2012; Charles et al., 1999; Godolphin, 2009; Makoul & Clayman, 2006).

Additional factors which can likely influence patients' understanding of DMD information were not fully explored by interventions in the present review. Patients' numeracy and literacy skills have the ability to modify understanding of the risks and benefits of treatments, with lower skills often leading to larger number of errors (Garcia-Retamero & Galesic, 2010a; Peters, 2008; Peters, Hart, & Fraenkel, 2011). This was only examined in one study within the present review, where patients unable to interpret numerical data demonstrated the least accuracy in understanding the treatment risk information even after intervention (Hofmann et al., 2012). Aspects of cognitive functions affected by MS itself are also likely to influence patient understanding, including: verbal and visual-spatial memory (Hulst et al., 2015; Langdon, 2011), information-processing speed (Goretti et al., 2014) and decision-making (Muhlert et al., 2015; Radomski et al., 2015). Yet only one interventional study monitored cognitive impairments of MS patients in the current review (Basso et al., 2010). This study showed that fictitious treatment understanding in MS patients with cognitive impairments was

considerably lower compared to MS patients who were cognitively intact. However, following additional cueing during intervention, the same level of understanding and recall was shown in cognitively impaired MS patients compared with cognitively intact MS patients (Basso et al., 2010). Hence, future interventions providing treatment information to MS patients may benefit from ensuring that patients of all abilities, and those presenting cognitive impairments due to MS, are able to benefit from the additional information given beyond routine healthcare.

2.4 General discussion

This chapter presents two systematic reviews to assess MS patients' understanding of the complex risk-benefit profiles of DMDs.

The first systematic review gathered evidence about patients' understanding of the risks and benefits of DMD within their standard healthcare, and their preferences for these risks and benefits. Despite the heterogeneous findings, it was evident that current ways of providing DMD risk and benefit information are not generally uniform or effective. MS patients tended to underestimate treatment risks and overestimate treatment benefits, with some patients finding comprehension especially difficult. MS patients preferred treatments offering extremely low levels of adverse risks, but were willing to accept higher risks in exchange for substantial long-term improvements.

This systematic review also showed that the ability to understand information about DMDs provided during the standard healthcare system was associated with certain patient factors, for example: age, education and functional status (Zimmer et al., 2015; Abolfazli et al., 2014). It is also possible that symptoms of MS itself, for example depression (Feinstein et al., 2014), anxiety (Hoang, Laursen, Stenager, & Stenager, 2015), fatigue (Khan et al., 2014) and cognitive impairments (DeLuca et al., 2015; D. W. Langdon, 2011), may further confound understanding of information about DMDs (see section 1.1.2 for review about MS symptoms). However, these symptoms were not

explored within the studies in the first systematic review. Nevertheless, it is apparent that some MS patients require further support to comprehend treatment information to a good standard.

The second systematic review was an inclusive attempt to compare different types of interventions which provide treatment information beyond routine healthcare, while evaluating their efficacy on understanding of treatment risks and benefits, and treatment decisions. Despite the heterogeneous findings from the second systematic review, it is conceivable to conclude that interventions providing treatment information beyond routine healthcare are preferred by MS patients and have the potential to improve understanding of overall treatment information, particularly treatment risks. Understanding of treatment benefits do not seem to be reliably improved by the reviewed interventions. There was no conclusive effect of interventions on MS patients' decision-making of DMDs. No particular intervention type emerged as reliably efficacious. Interventions that were longer and comprehensive performed similar to shorter interventions requiring fewer resources. There is a need for a standardised information-based tool which can draw on the strengths of currently available interventions and which can improve understanding of both the risks and benefits of treatments

The findings from both systematic reviews should be interpreted in line with the limitations. Firstly, it was difficult to draw robust conclusions or conduct a meta-analysis of the studies in both systematic reviews as a result of the variety of outcome measures employed. There were also differences in study design, methodology and patient characteristics between studies in both reviews which limits conclusions from such findings. This may indeed reflect the lack of uniformity across studies that address MS patients' understanding of medications. Secondly, a narrative synthesis was considered to be the most appropriate format for reviewing the studies across both systematic reviews. However, it is important to acknowledge that such a qualitative review is subject to

greater analysis bias than a quantitative systematic review. Finally, the reviews in the current chapter do not constitute an exhaustive search of studies or research findings; for example, the primary authors of studies were not contacted to resolve or expand on study findings owing to time and resource constraints. However, it seems unlikely that supplementary results or additional outcome measures could produce less heterogeneous results.

2.4.1 Conclusion

Systematic reviews carried out in the present chapter highlight that MS patients require extra support to effectively understand the complex risk-benefit profiles of MS DMDs, and that patients' preferences for treatment risks and benefits should be taken into account during the shared decision-making process. Interventions that have been designed to provide information about DMD risks and benefits beyond the standard healthcare system are appreciated by MS patients. Yet, interventions need to ensure that information is provided using effective presentation methods and that MS patients of all abilities and those presenting cognitive impairments can benefit from the additional support.

Chapter 3: Surveys of MS patients and MS Nurses in the UK

3.1 Introduction

A systematic review of the literature, which subsequently led to publication (Reen, Silber, & Langdon, 2017), found that MS patients do not satisfactorily understand the information they receive within standard healthcare (see chapter 2). The following chapter will explore in detail the current status of MS patients' understanding of DMD risks and benefits, and the sources that MS patients use to receive DMD information in the UK. It is expected that the following chapter will inform the need for evidence-based research in an attempt to improve treatment understanding of MS patients and identify the most suitable source to provide additional support.

3.1.1 Understanding of DMD risks and benefits

Patients' understanding of DMD risks and benefits is a prerequisite for making informed treatment decisions (Thompson, 2013). Accurate understanding of DMDs can increase engagement with the decision-making process and improve adherence to treatments (see section 1.3). Identifying unmet needs in clinics with regards to provision of DMD risks and benefits can help target support to MS patients and improve their understanding.

3.1.2 Sources of DMD risk and benefit information

Health professionals are often cited as the primary source of receiving information about DMD risks and benefits (Bishop, Frain, Espinosa, & Stenhoff, 2009). MS patients rate health professionals as an important and trustworthy source of information within healthcare services in Southern Australia (Matti, McCarl, Klaer, Keane, & Chen, 2010) and North America (Marrie, Salter, Tyry, Fox, & Cutter, 2013). Surveys conducted in the UK also find that MS patients prefer face-to-face provision of MS information (Hepworth & Harrison, 2004) and frequently meet with their health

professionals to receive DMD information (Somerset, Campbell, Sharp, & Peters, 2001). Hence, health professionals are often the leading contact and primary source of information provision for MS patients across healthcare services in different countries.

Patients also seek information about MS beyond that provided by health professionals. A widely used and reported source of information is the internet. Surveys designed to assess patients information-seeking habits find that MS patients frequently report searching online about their condition (Bishop et al., 2009; Hay, Strathmann, Lieber, Wick, & Giesser, 2008; Marrie et al., 2013), and in some studies patients report favouring the internet as a valuable source of MS information (Matti et al., 2010). Studies find that DMDs are researched the most by MS patients (Bishop et al., 2009; Marrie et al., 2013). In particular, the internet is regularly used to search for DMDs recommended by health professionals, new and available DMDs, and adverse risks associated with DMDs (Colombo et al., 2014). In fact, all MS patients in one study reported having used the internet in the past and considered it a useful resource for up-to-date information about DMDs (Synnot et al., 2014). Despite using the internet to independently seek information about DMDs, some MS patients also report feeling hesitant about the reliability of information available on the internet (Colombo et al., 2014; Synnot et al., 2014). This may be in part due to the range of websites available online that provide information about MS treatments. For instance, patients are able to access both objective information about DMDs through charitable websites, as well as subjective information about DMDs from online forums. Colombo and colleagues (2014) noted how MS patients distinguish between reliable and unreliable information on the internet. Questionnaires and focus groups with approximately 40 MS patients showed that if treatment information was equivalent across multiple websites or if the information available online was also reported by health professionals, this information was generally considered to be reliable. Information was also believed to be reliable if the website hosting the

information had existed for a long period of time (Colombo et al., 2014). This suggests that MS patients increasingly seek validated information about DMD risks and benefits on the internet.

Yet, the internet is rarely used as an isolated source of receiving information about DMDs. Online treatment information is largely used to supplement information received during consultations with health professionals, rather than to replace it. For instance, patients may search for information about DMDs prior to consultations with their physician or in order to better understand and collate information following consultations (Colombo et al., 2014). Other sources of information can also be used to complement the information about DMDs obtained from consultations, such as booklets and leaflets provided during visits to clinics. In fact, findings from an earlier systematic review about interventions to improve MS patients' understanding of DMDs, found that these interventions were designed to primarily be implemented in the form of booklets or via comprehensive educational programmes (Reen, Silber, & Langdon, 2017a). This means that interventions designed to provide additional support about DMDs have often implemented these using sources that are less frequently used by MS patients. The sources used to provide additional support to MS patients about DMDs should be carefully considered.

3.1.3 Service user involvement in research

Involving service users in research can improve the quality of patient-centred services and ensure that additional support for patients is targeted effectively (Crawford et al., 2002). A patient's experience about their condition and healthcare services can provide a complementary perspective to that of health professionals and researchers (see section 1.3 for review about patient-centred approach). Patient feedback can also offer valuable information in order to tailor existing healthcare services or design novel interventions to support patients in healthcare (Callard, Rose, & Wykes, 2012; Crawford

et al., 2002). Given the benefits of involving patients in research, the current chapter aims to explore the unmet needs of MS patients, and use patient responses to target appropriate additional support to MS patients.

Health professionals can also be involved in research to provide their experience of being a service provider to patients. In the context of MS, patients may interact with various health professionals including general practitioners, neurologists, physiotherapists, occupational therapists and nurses. It is therefore important to involve health professionals that most commonly provide information about DMDs to MS patients. Strickland and Baguley (2015) established that MS patients are most likely to network with MS nurses during the course of their disease in comparison to other health professionals in the UK. This may be because of the diverse role that a MS nurse plays within MS healthcare services. MS nurses are ordinarily responsible for providing psychosocial support, co-ordinating care, referring patients to other healthcare services, offering specialist advice and educating patients about their condition and medications (Forbes, While, Dyson, Grocott, & Griffiths, 2003; While, Forbes, Ullman, & Mathes, 2009). It is therefore important to involve MS nurses as service providers to compliment the feedback provided by MS patients.

3.1.4 Surveys as methods of involving MS patients and MS nurses in research

Effective involvement of service users in research inherently relies on the methods used to gather appropriate responses. According to general consensus in the literature, suitable approaches to acquire feedback from service users include qualitative interviews, focus groups and surveys (Crow, Gage, Hampson, Hart, Kimber, Storey & Thomas, 2002; Pope, Van Royen, & Baker, 2002; Wensing & Elwyn, 2003). Despite being comprehensive, focus groups and interviews can be time-consuming and research intensive to conduct. On the other hand, surveys have the ability to elicit similar levels of quality feedback without using as many resources (Cleary, 1999; Murphy, Mercer, Bruce,

& Eva, 2006; Pope et al., 2002). Notably, surveys can also be adapted to the research question of interest; surveys can either be quantitative in nature allowing for simple comparisons to be made between responses, or can be provided in a qualitative format allowing for detailed focus on patients' experiences (Jansen, 2010). In addition, surveys may be provided to service users at clinics to yield higher rates of responses or be sent anonymously to service users away from clinics to yield responses of a higher quality (Gribble & Haupt, 2005).

Overall, surveys offer ideal opportunities to obtain feedback from patients and health professionals. Surveys also offer several options to collect information; surveys can be quantitative or qualitative, and are able to elicit detailed responses if participants are given anonymity. For this reason, the present study employed surveys as the method of acquiring feedback from MS patients and MS health professionals in the UK.

3.1.5 Research questions

The aim of the present study was to investigate the unmet needs of MS patients in the context of information about DMDs, by conducting surveys with MS patients and MS nurses about MS healthcare services in the UK.

Four main points were explored in the present study:

- (i) MS patients' self-reported understanding of DMDs complemented by perspectives of MS nurses;
- (ii) the most common and preferred source to receive information about DMDs according to MS patients, complemented by perspectives of MS nurses;
- (iii) frequency of receiving information about DMDs in healthcare services according to MS patients, complemented by perspectives of MS nurses;

- (iv) feedback from both MS patients and MS nurses on how information provision about DMDs can be improved.

3.2. Methodology

3.2.1 Participants

MS patients were recruited from two hospitals in the UK: Queen Elizabeth Hospital as part of the Lewisham and Greenwich Trust, and King's College NHS Foundation Trust. MS patients were also recruited from the MS Trust charity. Patients were eligible to take part in the survey if they reported having a diagnosis of MS and were currently taking a DMD. MS nurses were recruited only from the MS Trust charity. MS nurses had no professional relationship with the recruited MS patients in the study. MS nurses were eligible to take part if they reported having consulted at least one MS patient.

No limit on the number of surveys distributed to both MS patients and nurses was applied due to the exploratory nature of the study. Patients and nurses were not compensated for their participation. Surveys for both MS patients and MS nurses received ethical approval from the Psychology Department Ethics Committee at Royal Holloway and the NHS Research Ethics Committee (see appendix 3 and 4).

3.2.2 Materials and design

The present study employed a cross-sectional survey methodology. Surveys for MS patients and MS nurses were author-developed for online and offline use (see appendix 5 and 6 for copy of offline MS patient and MS nurse survey). The online survey was hosted on the Qualtrics online survey platform and the offline surveys were distributed at hospital clinics. The survey consisted of both quantitative and qualitative questions with five distinct sections. The first section was designed to assess eligibility to take part in the study, and the remaining four sections related to the four research questions of interest. Questions that were not relevant for health professionals were

excluded from surveys distributed to MS nurses. Other than questions determining eligibility, patients were not required to answer all questions in the survey and therefore missing data was expected.

3.2.2.1 Survey section 1: Eligibility

The eligibility questions for MS patients assessed whether patients had been given a diagnosis of MS and were currently taking a DMD. Patients could only proceed with the survey if they responded affirmative to the MS diagnosis questions and stated their current medication. Patients were also encouraged to state duration of MS diagnosis and duration of taking the current DMD. Diagnosis information was also recorded for MS patients that did not report taking a DMD, but these patients were not eligible to complete the remaining survey. For surveys distributed to MS nurses, eligibility was determined by confirming whether nurses had conducted consultations with at least one MS patient in the past. If MS nurses responded with a yes, they were considered suitable to take part in the complete survey. MS nurses were also encouraged to state the duration of being a MS nurse.

Since surveys provided to both MS patients and MS nurses were anonymous, no other identifying demographic information was recorded.

3.2.2.2 Survey section 2: Understanding of DMD information

Questions about understanding of DMD information were split into two groups. First, questions 1-3 of the survey used 5-point Likert scales to determine how well patients felt they understood their current DMD, which ranged from 'slightly understood' to 'completely understood'. For MS nurses, the same question was stated in terms of how well they felt MS patients understood their DMDs. Three Likert scales were provided for: understanding of benefits, understanding of side-effects and understanding of the risks associated with DMDs. Both MS patients and MS nurses were provided with a qualitative

comment section immediately after each Likert-scale. In the second group, qualitative questions 9 to 13 were included at the end of MS patient surveys. These questions directly checked patients' knowledge about the benefits, side-effects and risks associated with their current treatment. Patients were further asked to state the risks and benefits they had experienced while taking the DMD. No corresponding questions were included in the surveys for MS nurses.

3.2.2.3 Survey section 3: Source of DMD information

Question 4 of both surveys required MS patients and nurses to state the source of DMD information they or their patients currently use, respectively. A choice of seven most-common sources of information were presented based on previous findings and respondents were encouraged to select all options that applied. An option of 'other' was also provided, and if selected, patients and nurses were required to specify the source of information not stated in the set of options provided. Both MS patients and nurses were then requested to comment on the usefulness of the selected sources of DMD information.

MS patients were further asked to state their preferences for all seven sources of DMD information in question 6 of the survey, excluding any other source of information that the patients reported using. Specifically, patients were asked to rate choices from 1 to 7, where 1 referred to the most preferred source and 7 to the least preferred source. A qualitative comment box was also provided for this question. No corresponding question was included in MS nurse surveys.

3.2.2.4 Section survey 4: frequency of DMD information provision

Both MS patients and nurses were asked to state, on average, how often information about DMD benefits, side-effects and risks were provided from a choice of 5 options: from 'every consultation' to 'in less than 1 in 10 consultations'. This was

question 8 of the MS patient survey and question 7 of the MS nurse survey. A qualitative comment section was also provided for this question.

3.2.2.5 Section survey 5: improvement of current ways of providing DMD information

Both MS patients (question 7) and nurses (question 5) were provided with one question to state how they believe current ways of providing DMD risk and benefit information could be improved.

3.3.3 Procedure

For patients recruited at hospital clinics, an information sheet and consent form was provided with the offline surveys (see appendix 7 and 8). If consent was given, patients were told they could either complete the survey during their clinic visit and hand back to the researcher, or take the survey home and mail to the researchers using the address provided. Patients were also informed that they could complete the survey online using the website address provided on the information sheet and at the end of the offline survey.

For surveys hosted online, both MS patients and nurses were provided with an online version of the information sheet to read prior to starting the survey (see appendix 9 and 10). Consent was assumed if both groups continued with the survey.

Since responses to the surveys were expected to inform all stages of the research and analysis, surveys were distributed to MS patients and MS nurses from September 2014 to December 2016.

3.2.4 Analysis

All data from offline surveys was transcribed by the researcher and combined with data from online surveys.

The quantitative data was analysed using frequencies and means as relevant. Missing quantitative data was excluded from analysis. Responses from the ordinal Likert

scales were collapsed into two categories: (i) completely understood, very well understood, and (ii) satisfactorily understood, moderately understood and slightly understood. For question 6 of MS patient surveys requesting patients to rate preference of source of DMD information, missing responses were rated as '0'.

For all qualitative data, main themes were derived and frequencies of these themes from patients and nurses were documented. No specific qualitative analysis was conducted as this was considered beyond the scope and exploratory nature of the present study.

3.3 Results

3.3.1 MS patient and MS nurse characteristics

A total of 106 MS patients completed the survey. Patients had been diagnosed with MS from within a year of taking the survey to 28 years, with average time since diagnosis of 8.08 years (SD: 7.34). The majority of patients were taking interferon betas as their current DMD (33.1%), followed by natalizumab (21.7%) and dimethyl fumarate (18.9%). Teriflunomide was taken by the least number of MS patients in this survey (1.9%). Patients had been taking their DMD medication from as recently as a few weeks to 19 years, with average duration of taking the DMD of 3.17 years (SD: 4.52).

A total of 146 patients who reported a diagnosis of MS were excluded from the study on account of reporting not taking a DMD. These patients had on average been diagnosed with MS for longer (mean: 12.60 years, SD: 10.57) than patients included in the study. In fact, majority of excluded MS patients had been diagnosed for over 20 years (26.1%). These patients are likely to have had the SPMS subtype of MS which currently has no licensed treatment (see section 1.1.3 for review of MS subtypes).

There are approximately 124,000 MS patients in the UK (Mackenzie et al., 2010) and around 80% of MS patients have reported seeing an MS specialist nurse within the last year according to the recent GEMSS report (2015). There are around 270 MS

specialist nurses in the UK (Mynors et al., 2012), which means that each MS specialist nurse sees approximately 360 MS patients per year. A total of 13 MS nurses were included in the current survey. Together, these nurses saw approximately 3,700 MS patients in the last year according to the above report. MS nurses in the survey reported being a specialist nurse from 2 years to 13 years, with an average experience of being a MS specialist nurse of 5.69 years (SD: 3.59).

3.3.2 Understanding of DMD information

3.3.2.1 Quantitative synthesis

Approximately half of all MS patients reported poor overall understanding of DMDs according to quantitative Likert-scales (see table 3.1). MS patients reported the least understanding of DMD risks (54.9%). In comparison, a greater percentage of MS nurses reported that patients do not understand information about DMDs in general, with lowest understanding of treatment benefits and side-effects (84%).

Table 3.1 MS patients' and MS nurses' feedback on patients' understanding of DMDs

		MS patient feedback (n=106)	MS nurse feedback (n=13)
Understanding of benefits	Good understanding, n (%)	56 (52.8)	2 (15.4)
	Poor understanding, n (%)	50 (47.2)	11 (84.6)
Understanding of side-effects	Good understanding, n (%)	54 (50.9)	2 (15.4)
	Poor understanding, n (%)	52 (49.1)	11 (84.6)
Understanding of risks	Good understanding, n (%)	46 (45.1) ¹	3 (23.1)
	Poor understanding, n (%)	56 (54.9) ¹	10 (76.9)

DMD, disease-modifying drug; ¹, n=102

When MS patients were clustered together in terms of DMDs they were currently taking, patients reported greatest understanding of alemtuzumab and lowest understanding of interferon betas. Specifically, MS patients reported the least

understanding of the benefits of interferon betas (62.9%) and dimethyl fumarate (55%), the least understanding of side-effects of teriflunomide (100%) and interferon betas (62.9%), and the least understanding of risks for alemtuzumab (100%), interferon betas (75%) and dimethyl fumarate (70%).

3.3.2.2 *Qualitative synthesis*

A qualitative synthesis was conducted for questions 8-10 of the MS patient survey which requested patients to report their understanding of benefits, side-effects and risks of their current DMD. The responses from patients that answered this question were grouped together and frequencies were recorded.

Reduction in relapse rate was the most commonly reported benefit of DMDs. However, approximately 40% of patients taking interferon betas did not report that their current DMD could reduce the rate of relapses. From an overview of the qualitative responses, the majority of patients did not report how much their DMDs were able to reduce the rate of relapses. The route of administration was further reported as a benefit of taking dimethyl fumarate (11.7%), fingolimod (8.3%), glatiramer acetate (12.5%), teriflunomide (100%) and natalizumab (9.1%), of which some treatments are taken orally and some treatments are taken by intravenous infusions.

Several side-effects of DMDs were reported by MS patients taking the survey. The most commonly reported side-effects for some of the DMDs were as follows: flu-like symptoms (46.4%) for interferon betas, flu-like symptoms (66.7%) and thyroid disorder (66.7%) for alemtuzumab, gastrointestinal problems (47.1%) for dimethyl fumarate, and injection site problems (50%) for glatiramer acetate. MS patients also reported understanding several risks of DMDs. The risk of PML was reported by the majority of patients taking natalizumab (77.3%), followed by low levels of immunity and serious infection for patients taking fingolimod (50%).

3.3.3 Source of DMD information

3.3.3.1 Quantitative synthesis

MS patients and nurses were asked to state all possible sources that MS patients used to receive information about DMDs. The majority of MS patients reported MS nurses (77.4%) and MS neurologists (65.1%) as their primary source of receiving information about DMDs (see figure 3.1). Similarly, MS nurses also stated that MS patients commonly speak with MS nurses (92.3%) and MS neurologists (100%) to receive information about DMDs (see figure 3.2). Other more common reported sources were booklets and charity websites according to both MS patients and MS nurses. The majority of MS nurses also reported patient websites as a frequently used source by patients, whereas only 24.5% of MS patients rated this as a source of information they currently use.

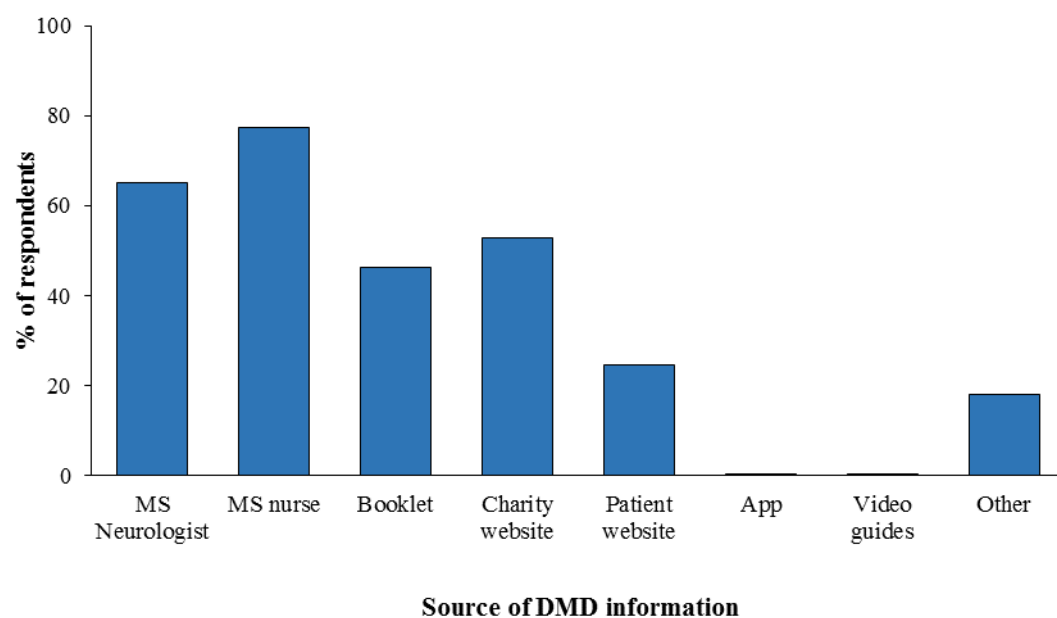


Figure 3.1 DMD information resources as reported by MS patients

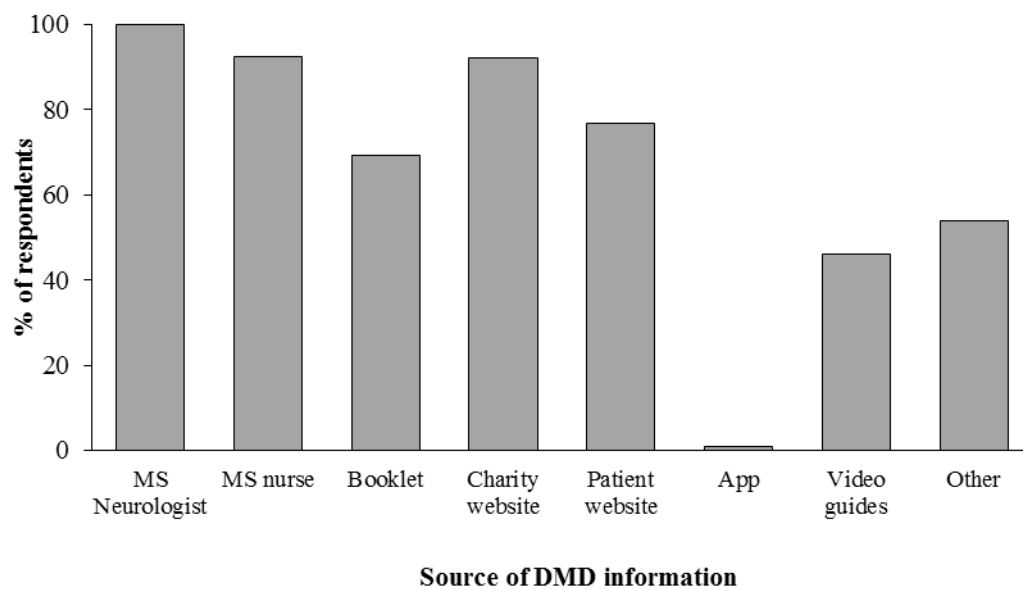


Figure 3.2 DMD information sources for patients as reported by MS nurses

3.3.3.2 Qualitative synthesis respondents

Approximately 17% of MS patients and 50% of MS nurses stated that other sources of DMD information provision were also used by patients. Qualitative synthesis of the main themes reported by MS patients and MS nurses identified 12 additional sources that patients use to receive DMD information (see table 3.2). These ranged from social media groups, online forums and scientific research papers, to personal experience of taking the DMD. Interestingly, 9 of the additional sources of DMD information reported by MS patients were not reported by MS nurses in this survey.

Main themes were also identified from qualitative questions asking MS patients and MS nurses to report the usefulness of all sources of DMD information they currently use. Approximately 57% of MS patients stated that the current sources used to receive information about DMDs was very useful. However, the remaining 43% of MS patients stated that they would like improvements to how they receive treatment information. The most common themes that emerged from qualitative responses of MS nurses to this

question were that multiple sources of information were often more useful for MS patients.

Table 3.2 MS patients' and MS nurses' qualitative feedback on additional sources used to receive DMD information

Other source of information, n (%)	MS patient feedback (n=19)	MS nurse feedback (n=7)
Social media group	6 (31.6)	0
Online forum	2 (10.5)	1 (14.3)
Friends/family	2 (10.5)	0
Patient contact helpline	1 (5.3)	0
Personal experience	1 (5.3)	0
Library	1 (5.3)	0
Other patients	2 (10.5)	3 (42.9)
Online blog	4 (21.1)	0
Research papers	3 (15.8)	0
NICE guidelines	1 (5.3)	0
Podcast	0	1 (14.3)
MS decisions	4 (21.1)	3 (42.9)

DMD, disease-modifying drug; NICE, The National Institute for Health and Care Excellence

3.3.4 Frequency of DMD information provision during consultations

3.3.4.1 Quantitative synthesis

MS patients and MS nurses reported the average number of consultations that were dedicated to providing information about DMDs to patients. A similar proportion of MS patients (37.4%) and MS nurses (38.5%) reported that patients receive DMD information at every consultation (see figures 3.3 and 3.4). However, a large number of MS patients also reported receiving DMD information in less than 1 in 10 consultations (24.2%), whilst no MS nurses reported that such few consultations were dedicated to information about DMDs.

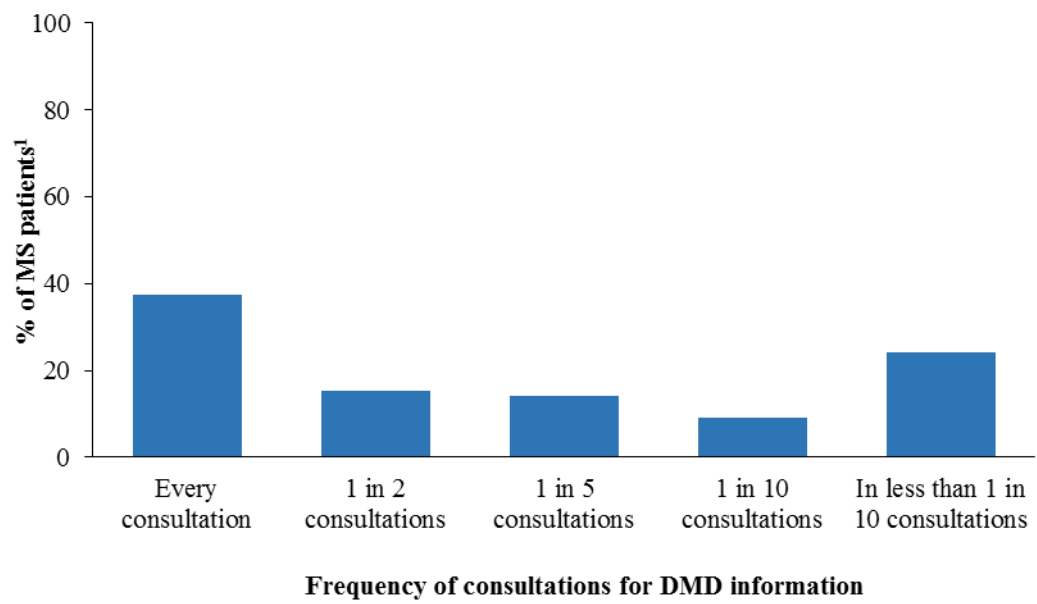


Figure 3.3 Frequency of consultations about DMDs as reported by MS patients; ¹ n=99

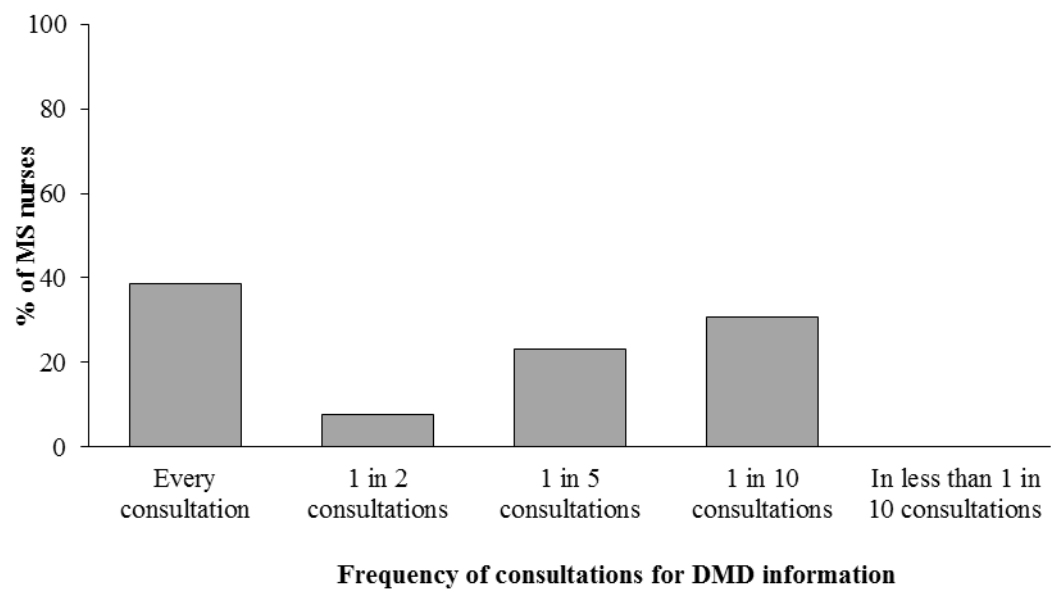


Figure 3.4: Frequency of consultations about DMDs as reported by MS nurses

3.3.5 Suggestions to improve DMD information provision

3.3.5.1 Qualitative synthesis

Main themes were derived from MS patients' and MS nurses' qualitative feedback on how DMD information provision could be improved. Of MS patients who answered this question, 13 different ways of improving DMD information were suggested (see table 3.3). The most common suggestions were providing more detailed and clear information about DMD risks and benefits (35.9%) and improving the consultations with health professionals (23.1%). The most common suggestion for improvement by MS nurses was that treatments should be provided such that patients are able to readily compare the risks and benefits (30.7%).

Table 3.3 MS patients' and MS nurses' feedback on improvement of DMD information provision

Possible improvements to DMD information provision, n (%)	MS patient feedback (n=39)	MS nurse feedback (n=13)
Patient-focused	2 (5.1)	0
Advice from experienced patients	3 (7.7)	0
Social media by health professionals	1 (2.6)	0
Booklet by independent bodies	1 (7.7)	0
Magazine articles	1 (2.6)	0
Clear information about risks and benefits	14 (35.9)	0
Standardised information	1 (2.6)	1 (7.7)
Case studies	1 (2.6)	0
Improved consultations with health professionals	9 (23.1)	1 (7.7)
Updated information about risks and benefits	3 (7.7)	1 (7.7)
Audiovisual presentation	1 (2.6)	0
Scientific/clinical trial information	1 (2.6)	2 (15.4)
Training of non-specialist health professionals	1 (2.6)	0
Interactive website	0	2 (15.4)
Application	0	1 (7.7)
Information sheets	0	1 (7.7)
Comparison of risks and benefits	0	4 (30.7)

DMD, disease-modifying drugs

3.4 Discussion

The current study sought to obtain feedback from MS patients and MS nurses about their experiences of how patients' receive information about DMDs in healthcare services across the UK. Surveys were used as a tool to collect both quantitative and qualitative data from service users in MS. Feedback was gathered to compliment a systematic review which found that MS patients do not satisfactorily understand the

DMD information they receive within their healthcare service (Reen et al., 2017). It was expected that exploring unmet needs of patients could ascertain how information about DMDs should be improved using evidence-based research. Four key research questions were explored: MS patients' current understanding of DMDs, the source that patients access to receive information about DMDs, the frequency with which DMD information is received and suggestions to improve current practices.

Approximately half of the MS patients in this study reported poor understanding of treatments, particularly the risks of DMDs. This finding was reinforced by MS nurses in the current study, as the majority of nurses reported that MS patients have poor understanding of DMD risks and benefits. This is consistent with studies included in the systematic review which recognised that many MS patients did not feel sufficiently informed about DMDs (Zimmer et al., 2015; de Seze et al., 2012; Heesen et al., 2003; Syed et al., 2014; Visser & Van Der Zande, 2011; Vlahiotis et al., 2010), and were poor at objectively understanding the treatment risks (Heesen et al., 2004; Hofmann et al., 2012; Köpke et al., 2014) and benefits (Mohr et al., 1996).

The benefits, side-effects and risks of interferon betas were the least understood by MS patients in the current study. This is of interest, given that interferon betas are typically offered to MS patients at the first stage of treatment and have well-established risk and benefit profiles (English & Aloï, 2015; Fogarty, Schmitz, Tubridy, Walsh, & Barry, 2016; Garg & Smith, 2015; Michel, Larochelle, & Prat, 2015; Wingerchuk & Weinshenker, 2016). It is possible that the safety profiles of interferons may be the reason why these treatments are not discussed in detail during consultations with health professionals compared to other drugs (see section 1.2 for review about risk-benefit profiles of interferon betas). This could be problematic for adherence to these commonly prescribed treatments. Evidence-based research should thus seek to facilitate understanding of information about all DMDs for MS patients.

MS patients reported accessing several sources to accumulate DMD information. The most commonly identified sources were consultations with MS neurologists and MS nurses, as well as access to charity websites. Similarly, MS nurses stated that MS health professionals and charity websites were commonly used by MS patients. An example of DMD information provided by charity websites, in the form of an online and offline booklet, is presented in appendix 11. Together, this data is consistent with previous survey findings which have identified health professionals and the internet as primary sources of obtaining information about DMD risks and benefits (Bishop et al., 2009; Colombo et al., 2014; Marrie et al., 2013; Matti et al., 2010; Synnot et al., 2014). Despite this, interventions that have been designed to provide additional support to MS patients have commonly employed booklets and comprehensive educational programmes to implement interventions (Reen et al., 2017a). To effectively promote MS patients' understanding of DMDs, future educational interventions should therefore be implemented using the most frequently accessed sources for information about DMDs.

Interestingly, questions about sources of DMD information also revealed discrepancies between MS patients and MS nurses. For example, despite majority of MS nurses stating patient websites as a commonly used method of receiving DMD information by MS patients, this was not reported by a large proportion of MS patients. In addition, there were differences in the additional sources used for receiving DMD information as stated by MS patients and MS nurses beyond those given in the survey. These disparities indicate that MS patients do not discuss their information-seeking behaviours with MS nurses during consultations. This, in turn, suggests that consultations could be improved by ensuring information is discussed between patients and health professionals in a clear and transparent manner.

MS patients reported very differently with regards to the frequency of receiving information about DMDs during consultations. Interestingly, a large proportion of

patients reported receiving information about DMDs at every consultation, with a similarly large number of patients reporting only having received information about DMDs in less than 1 in 10 consultations. Likewise, MS nurses' responses to the frequency of providing DMD information during consultations also varied considerably. One possibility for the variability amongst responses could be that information about DMDs are not provided to patients in a uniform or standardised manner across clinics. Given that all MS patients vary substantially in disease course and tolerability to DMDs, it is likely that patients are provided with information about DMDs based on their individual needs and stage of the disease. It is thus not possible to determine from the current study whether increasing the frequency of consultations for providing information about DMDs could improve patients' understanding of this information.

The current study identified a need for improving patient understanding about DMDs. By directly collecting suggestions from MS patients and MS nurses, it was possible to determine how provision of DMD information could be improved to meet the needs of patients and effectively target additional support, which is a recommended method by scientists advocating the involvement of service users in research (Callard et al., 2012; Pope et al., 2002). The most common suggestion offered by MS patients in this study was that detailed DMD risks and benefits should be clearly provided within healthcare services. Another suggestion was that the quality of consultations with health professionals should be improved. Moreover, MS nurses suggested that an effective comparison between DMD risks and benefits should be offered to patients seeking DMD information. It is reasonable to assume that applying these suggestions to current healthcare services could improve the way information is provided to MS patients about DMDs.

There are a number of limitations to the present study due to which the survey findings should be interpreted with caution. First, there was no attempt to statistically

analyse the quantitative information obtained from the surveys, and interpretations about the responses were not based on statistically significant results. Moreover, evidence-based qualitative analytical methods, such as a phenomenological analysis or a discourse analysis (Starks & Trinidad, 2007), were not employed in the current study, and themes from qualitative feedback were derived purely on the basis of frequency. Hence, conclusions based on both quantitative and qualitative data from the surveys are not statistically reliable. However, these analytical methods were deemed unsuitable and beyond the scope of the present study, considering that the primary purpose of the study was simply to determine unmet patient needs in the context of DMD information rather than conclusively establish how information about DMDs is provided to patients in the UK.

Second, it is not possible to determine the representativeness of participants in the current study. For MS patients, important demographic information such as age, ethnicity, education status, MS subtype, and level of disability was not recorded. These questions were excluded from the survey so that patients may provide comprehensive feedback about their experiences of MS clinics without feeling that they may be identified. However, in the absence of patient demographic information, it is not possible to determine whether the results obtained from the survey are truly representative of MS patients across the UK. In addition, there was an extremely low sample size of MS nurses in the current survey. The results from a small number of MS nurses was included as it was established that MS nurses in the current study would have consulted with approximately 3,700 MS patients in the last year and had experience of many consultations with MS patients (see section 3.3.1). However, it is important to acknowledge that the quality and style of consultations that are provided to patients may differ between MS nurses across the UK. Thus, the results obtained from MS nurses in

the current survey may be limited to the consultation styles of only a few nurses and not represent the types of consultations provided to most MS patients.

Finally, a selection bias may have been introduced in the current study which could further limit the representativeness of the sample. The majority of MS patients had been recruited from an online MS charity. These patients are more likely to have used online sources of information and be better informed than patients who are not members of an online charity. It is also possible that these patients were particularly interested in their condition and had access to other sources to receive treatment information. Yet, patients in the current survey still displayed limitations in understanding the risks and benefits of DMDs, which indicates that even patients with access to resources beyond consultations need additional support to better understand DMD information

3.4.1 Conclusion

In sum, the responses from the surveys employed in this survey indicate that not all MS patients feel satisfactorily informed about the risks and benefits of their DMD. The most common source of DMD information is through consultations with health professionals and searching the internet. In accordance with the suggestions offered by MS patients and nurses, future evidence-based research should focus on providing clear and accurate information about DMD risks and benefits, ideally during consultations with health professionals, in order to effectively improve MS patients' understanding of DMD risks and benefits.

Chapter 4: Verbal, numerical and graphical formats to present treatment information³

4.1 Introduction

Patients' understanding of treatment information is an integral part of shared decision-making within a patient-centred approach (see section 1.3). Systematic reviews of the literature (Reen et al., 2017) and surveys with MS patients and health professionals in the UK (see chapter 3), have established that MS patients are unable to satisfactorily understand the treatment information they receive. Several recommendations have been proposed in order to facilitate understanding in patients, including providing clear and accessible information using easily comprehensible presentation formats (Bunge, Mühlhauser, & Steckelberg, 2010; Edwards, Elwyn, & Mulley, 2002; Paling, 2003). These guidelines are largely based on evidence from studies with non-clinical populations or patients with conditions other than MS. Yet, interventions have been designed for MS patients in line with these guidelines. Notably, the methods used to present DMD risks and benefits in these interventions have been employed without directly evaluating these methods with MS patients (Reen et al., 2017a).

The following chapter will first identify the most optimal formats to present treatment risks and benefits to MS patients by reviewing studies conducted with different population groups, before reviewing the formats that have been evaluated directly with MS patients. Studies conducted with healthy, non-MS and MS clinical population groups will be used to identify the different types of formats that are used to present treatment information. The most common presentation formats from this review will then be empirically tested with MS patients in order to identify the best presentation formats to

³ The data from this experiment was presented as a poster at ECTRIMS conference, London, September 2016. The abstract developed for this conference was published as: Reen, G., Silber, E & Langdon, D. (2016). The influence of information presentation formats on treatment understanding and decision-making in MS patients. *Multiple Sclerosis Journal*, 22(S3), 884-917.

improve understanding of DMDs and reduce conflict in treatment decisions. Following this, a theoretical framework will be developed to demonstrate how MS patients' understanding of treatment information is likely to be affected by these formats.

4.1.1 Verbal formats

Medical information can be communicated verbally using a variety of commonly recognised terms, including anything from 'likely' to 'unlikely', or 'common' to 'rare' (Lipkus, 2007). European Commission (EC) guidelines recommend the use of specific verbal terms which are assigned to precise quantities when presenting information within treatment patient leaflets, and consist of: very common, common, uncommon, rare and very rare (EC Guidelines, 1998, 2009; see table 4.1). Verbal terms are also used to display DMD risk information in current clinical practises in the UK (see example in appendix 11). The following section will evaluate the use of verbal formats to denote treatment risks and benefits in studies with non-clinical and clinical populations.

Table 4.1 Verbal terms and assigned quantities as recommended by EC guidelines (1998, 2009)

Verbal terms	Assigned quantities
Very common	>10%
Common	1-10%
Uncommon	0.01 – 1%
Rare	0.01 – 0.1%
Very rare	< 0.01%

4.1.1.1 Evaluation of verbal formats in non-clinical populations

Studies evaluating the effectiveness of verbal formats to communicate quantitative information in non-clinical populations have produced mixed findings. Wallsten, Budescu, Zwick and Kemp (1993) conducted a large survey with students to record preferences about the best mode of communication. An equal number of

participants showed preferences for information communicated numerically and verbally. Verbal formats were preferred due to their ease of use, and their natural and personalised qualities (Wallsten et al., 1993). In another study, participants were presented with two scenarios which comprised uncertain but equivalent outcomes (Windschitl & Wells, 1996). Participants were randomly assigned to state the likelihood of an outcome occurring either using numbers or a verbal format (e.g. somewhat likely, very likely etc.). Findings showed that when using verbal terms, participants were more likely to state the correct likelihood of the outcomes occurring irrespective of the uncertainty. In subsequent experiments, Windschitl and Wells (1996) also found that employing verbal terms was better related with individual preferences for an outcome and behavioural intentions in comparison to employing numerical information. Windschitl and Wells (1996) concluded that verbal formats were more likely to encourage associative and intuitive thinking, and thus facilitate decisions based on uncertain outcomes. A similar conclusion was drawn by a review which found that individuals were more likely to make reasoned decisions when perceiving information in verbal formats (Moxey & Sanford, 2000).

In contrast, some studies have reported large variability in judgments when quantitative information is presented verbally to non-clinical populations. In an early study, participants were provided with a list of varying verbal terms (e.g. small probability, possible, great chance etc.) either in isolation or within different contexts (Brun & Teigen, 1988). Participants were required to assign a quantitative number to each format and state how much others would agree with their assignment in both conditions. The results showed large differences between participants when verbal terms were provided in context (e.g. a medical context), rather than in isolation. Individuals also underestimated the level of variability for each verbal format (Brun & Teigen, 1988). These findings pose a problem for verbal formats that could be provided within a treatment context, and also suggest that participants do not define verbal formats in the

same way. Critically, however, this study is not directly comparable with previous studies which showed benefits of employing verbal formats since different verbal phrases were used across all these studies.

It has been proposed that verbal phrases should be standardised and assigned to specific probabilities to avoid misunderstanding (Lipkus, 2007). For instance, guidelines by the European Commission (EC) have assigned specific quantities to verbal descriptors when communicating treatment risk information to patients: for instance, where ‘very common’ refers to over 10% patients experiencing a risk and rare referring to less than 0.01% patients who could experience a risk (EC Guidelines, 1998, 2009; see table 4.1). Studies have subsequently attempted to empirically test the efficacy of the verbal terms proposed by EC in the context of providing treatment risk information.

Berry, Knapp, and Raynor (2002) conducted two randomised studies with non-clinical population groups using hypothetical treatment information. The first study objectively examined the quantities that individuals assign to the five verbal terms recommended by the EC. All participants received all five verbal terms, but were randomised to either report back their numerical estimates as frequencies (e.g. 50 out of 10,000) or percentages (e.g. 5%). Participants were further randomised to receive information about either the minor risks of the treatment or severe risks of the treatment. Findings of the study showed large individual variability in interpretation of the five verbal terms, which could not be explained by the severity of the risk or how numerical estimates were made. These incongruities were particularly apparent for the terms ‘common’ and ‘very common’, as these were significantly overestimated in comparison to the actual quantities assigned by EC guidelines. In a follow-up study, participants also perceived the risks of the hypothetical treatment as increasingly severe and showed less intention to comply with treatments when the risks were presented using verbal terms in comparison to numbers (Berry et al., 2002). These findings converge with data from other

studies with large groups of non-clinical population, which found that treatment risks were poorly understood and significantly overestimated when presented using the verbal terms recommended by the EC (Berry, Raynor, Knapp, & Bersellini, 2004; Berry, Raynor, & Knapp, 2003).

The evidence reviewed thus far suggest that despite some mixed findings for the use of verbal terms to present quantitative information, numerical quantities assigned to verbal terms recommended by the EC guidelines are not clearly interpreted by non-clinical populations.

4.1.1.2 Review of verbal formats in clinical populations

The efficacy of verbal formats proposed by EC guidelines have further been assessed with clinical populations. In one study, Knapp, Raynor and Berry (2004) presented patients recovering from cardiac surgery with minor risks and adverse risks of two real medications in either verbal or numerical format. Patients were required to state the likelihood of the risks occurring, in addition to their perceived risk severity and their decision of whether to take the medication. The findings showed that both minor risks and adverse risks of medications were overestimated when presented in the verbal formats proposed by EC guidelines. Further, patients were more likely to perceive the risks as higher and decide against the medication when the risks were presented in verbal formats, indicating that poor understanding could lead patients to make inappropriate treatment decisions (Knapp et al., 2004).

It has been suggested that understanding of verbal formats may be improved if accompanied by numerical information (Lipkus, 2007). In fact, the most recent EC guidelines (2009) strongly recommend the use of verbal formats alongside the correct numerical quantity, if available (see table 4.1). Knapp and colleagues (2009) examined these recommendations by randomly allocating cancer patients to three possible formats of presenting treatment risk information: verbal formats, numerical formats, or a

combination of verbal and numerical formats. Data from this study showed that patients were not able to accurately understand treatment risks when presented verbally, in comparison to numerically presented information. Interestingly, patients also showed poor understanding when treatment risks were presented using a combination of both verbal and numerical formats (Knapp et al., 2009), supported by a more recent version of the study (Knapp, Gardner, & Woolf, 2015).

Overall, findings from this section indicate that verbal descriptors are not clearly understood by both non-clinical and clinical population groups, even when accompanied with numerical quantities as recommended by EC guidelines. These verbal terms are used in current clinical practise in the UK (see appendix 11). Yet, no studies to date have evaluated the efficacy of presenting treatments using verbal terms to patients with MS. For this reason, verbal formats were incorporated into the theoretical framework of factors that could affect MS patients' understanding of treatments (see figure 4.1).

4.1.2 Numerical formats

Treatment risks and benefits can also be conveyed to patients using numerical information. The most commonly used numerical formats to present information in a medical context are percentages (e.g. 5%) and frequencies (e.g. 20 events observed out of 100). Both frequencies and percentages are employed in UK clinical practises to provide DMD risks and benefits to MS patients (see appendix 11).

Numerical information has several positive qualities, such as precision, scientific credibility and the ease in which numbers can be converted from one form to another (e.g. frequencies to percentages) (Lipkus, 2007). In fact, people generally prefer numerical formats based on these qualities (Gurmankin, Baron, & Armstrong, 2004; Wallsten et al., 1993), although numerical formats are also considered to be impersonal relative to information presented verbally (Ancker, Chan, & Kukafka, 2009; Wallsten et al., 1993). With respect to understanding the information, numerical formats are consistently shown

to be superior in comparison to verbal formats (Berry et al., 2004; Berry et al., 2003; Berry et al., 2002; Windschitl & Wells, 1996). These studies, however, also show that understanding between different numerical formats can vary. To examine which numerical format can maximise understanding of treatment risk and benefit information in MS patients, the following section will review findings from studies conducted with both non-clinical and clinical populations.

4.1.2.1 Review of numerical formats in non-clinical populations

A number of studies have assessed the effects of frequencies and percentages on understanding of a screening test problem with both physicians and the general population (Bramwell, West, & Salmon, 2006; Gigerenzer, 1996; Hoffrage & Gigerenzer, 1998; Mellers & McGraw, 1999) (see table 4.2 for an example of the screening test problem). Based on this problem, participants were required to state the number of patients that could have breast cancer after a positive mammography screening result. Overall understanding of the screening test problem was poor across all studies, likely due to inferences and calculations required in order to correctly arrive at the answer. However, both physicians and the general population consistently showed better understanding when the screening test problem was presented in frequencies rather than percentages (Bramwell et al., 2006; Gigerenzer, 1996; Hoffrage & Gigerenzer, 1998; Mellers & McGraw, 1999). Whilst these findings indicate that medical information presented in frequencies are easier to interpret, understanding the likelihood of detecting a disease may be different to understanding the risks and benefits of a treatment.

Table 4.2 The screening test problem in frequencies and percentages, as adapted from Gigerenzer and Edwards (2003)

Numerical format	Screening test problem
Percentages	The probability that a woman has breast cancer is 0.8%. If she has breast cancer, the probability that a mammogram will show a positive result is 90%. If a woman does not have breast cancer the probability of a positive result is 7%
Frequencies	Eight out of every 1000 women have breast cancer. Of these eight women with breast cancer seven will have a positive result on mammography. Of the 992 women who do not have breast cancer, some 70 will still have a positive mammogram.

The effect of frequencies and percentages in the context of treatment risk and benefit information has been evaluated by Waters, Weinstein, Colditz, and Emmons (2006). Participants were presented with a hypothetical risk of cancer for which a treatment could reduce the risk to a certain degree but with a potential risk of developing another type of cancer. Understanding was measured by asking participants whether their total cancer risk would increase, decrease or remain the same. The findings showed that treatment risk and benefit information presented in percentages was better understood than information presented in frequencies (Waters et al., 2006). Similar findings were obtained by Woolshin and Schwartz (2011), as they randomly presented participants with treatment risks and benefits in frequencies, percentages, or a combination of percentages and frequencies. Participants showed greater understanding of treatment risks and benefits when provided in percentages compared to frequencies. Understanding of treatment risks and benefits when presented in a combination of the two numerical formats was equivalent to that of percentages (Woolshin & Schwartz, 2011). Interestingly, two types of frequencies were presented in this study. For one frequency, the denominator remained constant (e.g. 4 out of 1000, 10 out of 1000), whereas for the

other frequency, the numerator remained constant at 1 (e.g. 1 out of 10, 1 out of 100). To explain why neither of these frequencies improved understanding, Woolshin and Schwartz (2011) proposed that small frequencies may be magnified when the denominator is kept constant, whereas the denominator is likely to be ignored when only the numerator is kept constant.

In short, providing medical information numerically improves understanding in non-clinical populations in comparison to information presented verbally. However, it is unclear to what extent understanding can be improved when presented in specific numerical formats. In fact, some studies show no effects on understanding when treatment risks and benefits are presented in either frequencies or percentages (Cuite, Weinstein, Emmons, & Colditz, 2008; Gurmankin et al., 2004; Peters et al., 2011). Although, it is possible that understanding may differ for population groups that are more likely to make treatment decisions based on treatment information. Thus, findings based on clinical population groups need to first be reviewed prior to drawing any conclusions about the efficacy of different numerical formats.

4.1.2.2 Review of numerical formats in clinical populations

Chapman, Litton, Chamberlain and Ho (2015) used surrogate decision-makers to assess perceived risk of treatment presented in different numerical formats. Surrogate decision makers in this study were the next of kin of critically ill patients and responsible for making medical decisions for patients. Participants were randomised to hypothetical treatment scenarios, with information in one scenario presented in percentages (e.g. 20% risk of death) and information in the other scenario presented in frequencies (e.g. 1 in 5). Participants were then required to state the perceived risk of death on a visual analogue scale. The study found that the risks were consistently interpreted as higher when presented in frequencies rather than percentages, suggesting a difference in understanding

between these formats. Note, however, that objective understanding was not measured in this study.

In another study, Bramwell and colleagues (2006) provided women who were pregnant with the potential risk of their child having Down's syndrome following a screening test. Women were randomly assigned to information presented in either frequencies or percentages. To note, the structure of the information presented to women was similar to that of the screening test problem reviewed previously (see table 4.2). When women were assessed on the likelihood their child having a risk of the condition following a positive result on the test, the majority of women were not able to accurately answer the question. However, of women who had answered questions correctly, there was a trend for information to be better understood when presented in frequencies in comparison to percentages although this finding was nonsignificant.

In summary, the effects of presenting treatment risk and benefit information in frequencies or percentages on understanding remains inconclusive based on findings with physicians, patients likely to make healthcare decisions and the general population. This is supported by reviews of the literature which did not find any format to be more reliable at improving understanding of treatment information (Lipkus, 2007; Zipkin et al., 2014). Despite these heterogeneous findings, recommendations have been made for the use of frequencies when presenting medical information to patients primarily based on the screening test problem (Akl et al., 2011; Bunge et al., 2010), which needs to be interpreted with caution when communicating treatment risks and benefits to patients. In addition, no study to date has directly tested the impact of frequencies and percentages on understanding of treatments with MS patients. These formats were therefore included into the theoretical framework of MS patients' understanding (see figure 4.1).

4.1.3 Graphical formats

Treatment risks and benefits can also be represented visually through the use of graphical formats, such as bar charts, line graphs, pie charts and pictographs. The positive qualities of graphical formats include their ability to summarise large data and reveal patterns that would otherwise go undetected (Lipkus, 2007). In fact, when numerical information is accompanied by visual formats, patients' accuracy of risk perception can be facilitated more so than numbers alone (Garcia-Retamero & Galesic, 2010b; Garcia-Retamero & Hoffrage, 2013; Tait, Vopel-Lewis, Zikmund-Fisher, & Fagerlin, 2010). This has been supported by a review of the literature which found that all types of visual presentations generally facilitate patients' understanding of medical information (Bunge et al., 2010). Nonetheless, not all graphical formats have the same effects on understanding of treatment risks and benefits. The following section will explore the effects of particular graphical formats on understanding treatment information with both non-clinical and clinical populations, prior to discussing the limited findings with MS patients.

4.1.3.1 Review of graphical formats in non-clinical populations

A number of studies have assessed preferences of specific graphical formats with non-clinical populations. Using a qualitative methodology, Schapira, Nattinger and McHorney (2001) compared horizontal bar charts, vertical bar charts and pictographs displaying highlighted figures corresponding to the risk of treatment, in a non-clinical population. The human figures in these pictographs were either highlighted consecutively or randomly arranged. Schapira and colleagues (2001) found that vertical bar charts were unanimously favoured in comparison to horizontal bar charts. However, the most preferred visual format for the majority of participants was the consecutively arranged human-figured pictographs. In contrast, the random highlighted pictographs were considered too cognitively difficult to comprehend. Interestingly, participants still

reported randomly arranged formats as being more ‘true’ than those arranged consecutively (Schapira et al., 2001). Likewise, the positive comments for randomly arranged pictographs outnumbered the negative comments in another qualitative study (Ancker et al., 2009). Together, these studies indicate that people interact with treatment risk information differently depending on the graphical formats used to represent the information. Critically, however, it is not possible to determine how understanding is affected simply based on preferential judgments. Subsequent studies with objective measures have shown that medical risks are actually overestimated when presented using pictographs with human figures highlighted at random (Schapira, Nattinger, & McAuliffe, 2006), despite some preference for these formats (Ancker et al., 2009; Schapira et al., 2001).

A number of studies have objectively assessed understanding of medical risk information when presented in different graphical formats. Brewer, Gilkey, Lillie, Hesse and Sheridan (2012) conducted two experiments to assess preferences and accuracy of understanding of bar charts and tables to present information about hypothetical medical test results. In the first experiment, participants were assigned to either the bar chart or table condition (between subjects), whereas the second experiment presented participants with both graphical formats (within subjects). Participants in both experiments performed equally well on measures of understanding and showed no preferences for either format (Brewer et al., 2012). Conversely, when tables were compared to pictographs in another study, understanding was found to be greatest for pictographs (Tait et al., 2010). More recently, Hamstra and colleagues (2014) evaluated four different types of graphical formats against each other, consisting of line graphs, pie charts, bar charts and pictographs. Participants were assessed on verbatim and gist understanding of the hypothetical risk of developing prostate cancer. Understanding was the greatest for bar charts and pictographs, and poorest for line graphs and pie charts (Hamstra et al., 2014).

Despite these findings showing clear differences in understanding when medical information is presented in different graphical formats, it is possible that information about treatment risks and benefits may be understood differently.

Some studies have evaluated graphical formats in a treatment context. Tait, Voepel-Lewis, Brennan-Martinez, McGonegal and Levine (2012) examined the effects of pie charts, bar charts and pictographs to present treatment risks and benefits. Participants did not show differences in understanding of treatment risks and benefits presented in different graphical formats, although pictographs and bar charts were preferred more than pie charts. Interestingly, this study did find that participants presented with graphical formats for which they previously stated a preference, showed the greatest understanding and satisfaction in comparison to participants who were not provided with their preferred graphical format (Tait et al., 2012). In another study, McCaffery and colleagues (2012) compared the effects of presenting treatments using both pictographs and bar charts on understanding in a non-clinical population. Participants showed better understanding for pictographs when treatment risks were low (e.g. 100 out of 1000), whereas bar charts were better understood for medium to large levels of risk (e.g. 500 out of 1000) (McCaffery et al., 2012). Bar charts were preferred the most even though this did not influence performance, unlike the study by Tait and colleagues (2012). Another study provided non-clinical populations with hypothetical treatment risks and benefits in six different graphical formats (Hawley et al., 2008). These formats consisted of: pie chart, bar chart, pictograph, modified pictograph, modified pie chart and table. Participants were assessed for their verbatim and gist understanding using a number of comprehension questions. Findings showed that tables and bar charts were more effective at increasing verbatim accuracy of hypothetical treatment risks and benefits, even though people had poor gist understanding of treatments. The table was rated as the most effective and scientific graphical format. Notably, pictographs performed consistently well on all

variables in this study; both verbatim and gist knowledge was high and the graph was also strongly preferred by people in the study. Hawley and colleagues (2008) thus concluded that pictographs are an ideal graphical format to present treatment risks and benefits to individuals.

Taken together, studies with non-clinical populations indicate that individuals perceive medical and treatment risks and benefits differently when this information is represented in various graphical formats. Bar charts, tables and pictographs seem to greatly improve understanding in comparison to other graphical formats. However, reliable conclusions cannot be drawn from these findings given that the graphical formats compared in studies vary greatly.

4.1.3.2 Review of graphical formats in clinical populations

Only very few studies have examined different graphical formats on understanding of medical information in clinical populations. Garcia-Retamero and Hoffrage (2013) evaluated the efficacy of pictographs to present the screening test problem (see table 4.2 for example) to patients recruited from a primary health care service. In comparison to the screening test problem presented only in frequencies, patients that were also provided with pictographs showed significant improvements in their ability to solve the problem. Similarly, Zikmund-Fisher and colleagues (2008) employed pictographs to represent treatment information with the total pictograph referring to either 100 people or 1000 people. Real treatment risks were communicated to women with elevated risk of breast cancer going through consultations at health clinics. Understanding of treatment risks was shown to be high when information was presented in pictographs, regardless of the total figure size, in comparison to when information was only presented in frequencies (Zikmund-Fisher et al., 2008).

In sum, very few studies have been conducted with clinical populations to evaluate the efficacy of graphical formats. Of these, comparisons were limited to

pictographs and frequencies, with pictographs improving understanding the most. Studies comparing different types of graphical formats in clinical populations are thus lacking.

4.1.3.3 Review of graphical formats in MS patients

With regards to MS, only one study has assessed the efficacy of graphical formats to present treatment risk and benefit information. Similar to other findings in the clinical literature (Garcia-Retamero & Hoffrage, 2013; Zikmund-Fisher, Ubel, et al., 2008), the study by Kasper, Heesen, Köpke, Mühlhauser and Lenz (2011) only assessed the effectiveness of pictographs in communicating the risks and benefits of hypothetical treatments in MS. Yet unlike previous findings, Kasper and colleagues (2011) found that MS patients were not able to understand the treatment risks when presented with human-figured pictographs, in addition to significantly overestimating the treatment benefits. Whilst the effects found in this study were only based on hypothetical treatments and may not necessarily correspond to risk and benefits of actual MS medications (Kasper et al., 2011), the fact that pictographs do not have the same effect on MS patients' understanding in comparison to other studies poses a problem for adopting methods from studies with non-clinical populations to healthcare practises.

4.1.3.4 Additional elements in graphical formats

The elements in graphical formats can also influence understanding of treatment information, as demonstrated by studies conducted predominantly with non-clinical populations. These elements include numerical formats added to graphical formats, orientation of graphical formats, pictograph arrangement and the type of figures used within pictographs.

Reviews of the literature recommend that visual aids and numbers should be provided together to maximise understanding of medical information in patients (Bunge, Mühlhauser, et al., 2010; Lipkus, 2007). In fact, Hamstra and colleagues (2014) found

that frequencies added to pictographs significantly improved understanding in comparison to presenting information using graphical formats alone. These findings were further supported by Hawley and colleagues (2008), as understanding was shown to improve when graphical formats also displayed numerical frequencies. Conversely, when a combination of graphical formats and frequencies to present treatment information was compared with numerical formats alone, no differences in understanding information was observed in a group of non-clinical populations (Henneman et al., 2013). Thus, whether numbers and graphical formats presented together can improve understanding of treatment risks and benefits more than numerical or graphical formats presented alone need to be examined further.

Vertically oriented graphical formats have also been shown to improve understanding compared to graphs orientated horizontally, irrespective of the graphical format itself, i.e. vertical pictographs and bar charts were considered more effective than horizontal pictographs and bar charts, respectively (McCaffery et al., 2012). Likewise, vertical bar charts led to fewer comprehension errors in comparison to horizontal bar charts presenting medical information in other studies (Feldman-Stewart, Kocovski, McConnell, Brundage & Mackillop, 2000). In contrast, Price, Cameron and Butow (2007) found that accuracy of understanding was greater for horizontal pictographs as opposed to pictographs orientated vertically, suggesting that the impact of graph orientation on understanding is uncertain.

Treatment information displayed in pictographs can also be represented using different types of figures, which range from human faces and human bodies, to abstract symbols such as ovals and rectangles. Although results from various studies have favoured the use of pictographs, the figures employed in pictographs across studies tend to vary considerably. Zikmund-Fisher and colleagues (2014) directly compared six different types of figures on participants' understanding and preferences. Understanding

was greatly improved for all anthropomorphic figures (i.e. outline of human bodies, outline of human heads and photos of humans) in comparison to abstract figures. The most preferred pictograph figure was the outline of human bodies (Zikmund-Fisher et al., 2014). Yet, no difference in understanding emerged between human or abstract pictographs for individuals with poor numeracy skills (Zikmund-Fisher et al., 2014). Similarly, no differences were observed in risk perception when participants were presented with human figures or abstract figures in pictographs within another study (Schapira et al., 2006), indicating a need to further examine the effects of different figures in pictographs on understanding of medical information.

Relatedly, the figures within pictographs can either be arranged consecutively or randomly to represent the number of people affected by a risk or benefit. Random arrangement in pictographs are often considered to be more realistic as they represent the randomness of patients who may be affected by a treatment risk or experience a treatment benefit (Ancker et al., 2009; Schapira et al., 2001). Despite this, participants also describe randomly arranged figures as too visually complex to comprehend (Schapira et al., 2001) and generally overestimate the risks when pictographs are presented randomly rather than consecutively (Schapira et al., 2006). The impact of pictograph arrangement on understanding treatment information has in fact been conducted with MS patients in one study (Kasper et al., 2011). Although consecutively arranged pictographs were strongly preferred by MS patients, there were only very small differences between understanding of treatment risks and benefits between these different arrangements (Kasper et al., 2011).

In summary, understanding of medical information can vary depending on how information is presented graphically to both non-clinical and clinical populations. Studies conducted with clinical populations, including patients with MS, have generally only assessed the effectiveness of pictographs as graphical tools to present medical information. For this reason, it is important that research with MS patients compares

different graphical formats in order to determine which graphical format is able to maximise understanding of treatment risk and benefit information. Moreover, studies conducted largely with non-clinical populations have shown that different elements of graphical formats may further influence understanding of treatment risks and benefits. Aside from arrangement of pictographs, other elements of presenting graphical formats have not been examined in MS populations on their understanding of the risks and benefits of treatments. With these findings in mind, graphical formats were also incorporated into a theoretical framework of MS patients' understanding (see figure 4.1).

4.1.4 Patient understanding and patient characteristics

The ability to accurately understand treatment risk and benefit information from verbal, numerical and graphical formats can also be dependent on patient characteristics. These characteristics are reviewed in some detail below and are also included into the theoretical framework of MS patients' understanding.

4.1.4.1 Numerical reasoning, health literacy and premorbid IQ

Numeracy skills, health literacy and IQ are individual characteristics closely related with level of education (Peters, 2008). These skills are likely to influence how treatment information from different formats is understood.

Participants with poor numeracy skills experience difficulty in understanding medical information provided in percentages compared to information presented in frequencies. The absence of these differences in highly numerate individuals thus signifies that numeracy skills can impact interpretation of information presented in certain numerical formats (Peters et al., 2011). It has been proposed that individuals with poor numeracy skills may benefit from numerical information presented alongside graphical formats (Lipkus, 2007; Paling, 2003). This is supported by studies showing that graphical formats can significantly improve understanding of information for low numerate individuals (Garcia-Retamero & Galesic, 2010b; Hamstra et al., 2014). Understanding

information presented in specific graphical formats has also shown to be dependent on individuals' numeracy skills. Hawley and colleagues (2008) found that participants with high numeracy scored significantly higher on comprehension questions for all graphical formats. However, for respondents with weaker numeracy skills, information presented in pie charts, tables and pictographs was better understood in comparison to all other graphs. Likewise, during comparison of different pictograph figures, Zikmund-Fisher and colleagues (2014) found that participants with poor numeracy skills misunderstood risk information when presented with human figures, unlike patients with greater numeracy skills.

Overall, studies with non-clinical populations indicate that patients' numeracy skills may affect understanding of treatment risk and benefit information when presented using a range of numerical and graphical formats. Studies did not examine the impact of health literacy or IQ for treatment information presented using these formats. Regardless, it is conceivable that health literacy and IQ can also affect how treatment information is understood from different verbal, numerical and graphical formats.

4.1.4.2 Symptoms of MS

Understanding of treatment information presented in different verbal, numerical and graphical formats may be influenced by symptoms of MS. Clinical opinion holds that particular MS symptoms, such as fatigue, mood and cognitive impairments, are likely to influence understanding of treatment information (Chiaravalloti & Deluca, 2008; Langdon, 2011) (see section 1.1.2 for review about MS symptoms). Non-clinical participants have reported that complex formats, such as randomly arranged pictographs, tend to increase cognitive load and thus are difficult to comprehend (Schapira et al., 2001). Therefore, it is expected MS patients experiencing cognitive impairments in particular may show differences in understanding treatment information when presented in different verbal, numerical and graphical formats.

4.1.5 Patient understanding and decisional conflict

Patients' understanding of treatments can lead to informed treatment decisions (see section 1.3 for review). It is therefore expected that patients may experience conflict in their treatment choice if treatment information is not accurately understood. Decisional conflict is especially likely when patients are confronted with uncertainty of outcomes, the risks and benefits for each outcome varies considerably, and there is a need to make trade-offs between acceptable levels of risks and benefits (Janis & Mann, 1977; O'Connor, 1995). These conditions are likely in a chronic condition such as MS, as patients making the decision to take a DMD are confronted with complex risk-benefit profiles and the impact of treatments on an individual's disease course is often unclear (see section 1.2). Thus, MS patients making decisions about the most suitable DMD are likely to experience conflict in their decisions.

Decisional conflict can be measured by the Decisional Conflict Scale (DCS) (Janis & Mann, 1977; O'Connor, 1995). The DCS is generally considered a reliable and validated measure which discriminates between patients who are conflicted in their decisions and those who are not conflicted in their treatment choice (O'Connor, 1995; Stacey et al., 2014). The scale assigns patients an overall decisional conflict score, which is a composite of the scores on the following five measures: uncertainty in choosing between available options, perception of feeling informed about the risks and benefits of each option, personal values towards benefits and risks of options, level of perceived support during decision-making and the likelihood of implementing the chosen option (O'Connor, 1995; Stacey et al., 2014). Thus, a greater score on the overall DCS and the DCS subscales pertains to a high level of conflict in patients' decisions.

Despite poor understanding of available options considered as one contributing factor of patients' conflict in their decisions, studies that have assessed the relationship between patients' understanding of treatment choices and patients' decisional conflict

have produced inconsistent findings. A small significant inverse correlation between understanding and overall decisional conflict was reported in the DCS validation study, indicating that as understanding increases the conflict in decisions tends to reduce albeit by a small margin (O'Connor, 1995). However, other studies have demonstrated a higher significant inverse relationship between understanding of treatment information and decisional conflict, with both the overall DCS score (Cormiers, Legare, Simard, & Boulet, 2015) and scores on the DCS subscale which assesses patients' perception of being informed (Sun, 2005). On the other hand, several studies have examined an indirect relationship between understanding and decisional conflict by independently examining both outcomes following interventions designed to improve patients' healthcare decisions. Some interventions have demonstrated both improvements in understanding and reduction in overall decisional conflict (Arterburn et al., 2011; Evans et al., 2010; Nassar, Roberts, Raynes-Greenow, Barratt, & Peat, 2007; Wong, Thornton, Gbolade, & Bekker, 2006), whilst other interventions only showed improvements in understanding but with no apparent reduction in overall decisional conflict (Köpke et al., 2014; Leighl et al., 2011; Mann, Ponienman, Montori, Arciniega, & McGinn, 2010; Schapira et al., 2007). When interventions were pooled together into a review, both understanding was improved and decisional conflict was reduced in clinical populations (Stacey et al., 2014). Given that such interventions are often designed by integrating several different factors, it is not possible to assess whether there was a direct relationship between understanding and decisional conflict or whether a relationship was moderated by components of the intervention.

In summary, accurately understanding treatment risks and benefits is likely to reduce decisional conflict in MS patients. Decisional conflict can generally be measured using the DCS measure. Although findings are inconsistent, patients' understanding tends to directly and indirectly reduce conflict in treatment decisions. It therefore remains to be

explored whether this relationship holds for MS patients attempting to understand treatment information using verbal, numerical and graphical formats.

4.1.6 Research questions and hypothesis

The following experiment addressed five important research questions motivated by the review of the literature. First, can verbal formats maximise understanding of treatment risk and benefit information compared to numerical formats? Second, which numerical format (frequencies or percentages) can maximise understanding of treatment risk and benefit information in MS patients? Third, which graphical format can maximise understanding of treatment risk and benefit information in MS patients? Fourth, which additional elements can be added to graphical formats (orientation, pictograph figures, pictograph arrangement and numbers displayed on graphical formats) in order to maximise understanding of treatment information in MS patients? Finally, what is the relationship between MS patients' understanding of treatments presented in different formats with patients' conflict in treatment decisions? Additional exploratory questions attempted to address how patients' numerical reasoning, health literacy and symptoms of MS could impact MS patients' understanding of treatments presented in different formats?

Hypotheses for the following experiment was generated from the literature and were as follows:

- (i) Numerical formats will maximise understanding of treatment information in comparison to verbal formats;
- (ii) Frequencies and percentages will have the same effect on patients' understanding;
- (iii) Pictographs would maximise understanding of treatment information compared to other graphical formats (bar charts, line graphs and pie charts);

- (iv) All graphical formats with numbers displayed would maximise understanding of treatment information;
- (v) Orientation of graphical formats will show no difference in patients' understanding;
- (vi) Human figures on pictographs will maximise understanding compared to abstract shapes on pictographs;
- (vii) Consecutively arranged pictographs will maximise understanding compared to randomly arranged pictographs;
- (viii) Greater understanding of treatment information will be related to reduced conflict in treatment decisions by MS patients;
- (ix) Numerical reasoning will be positively related with understanding of treatment information.

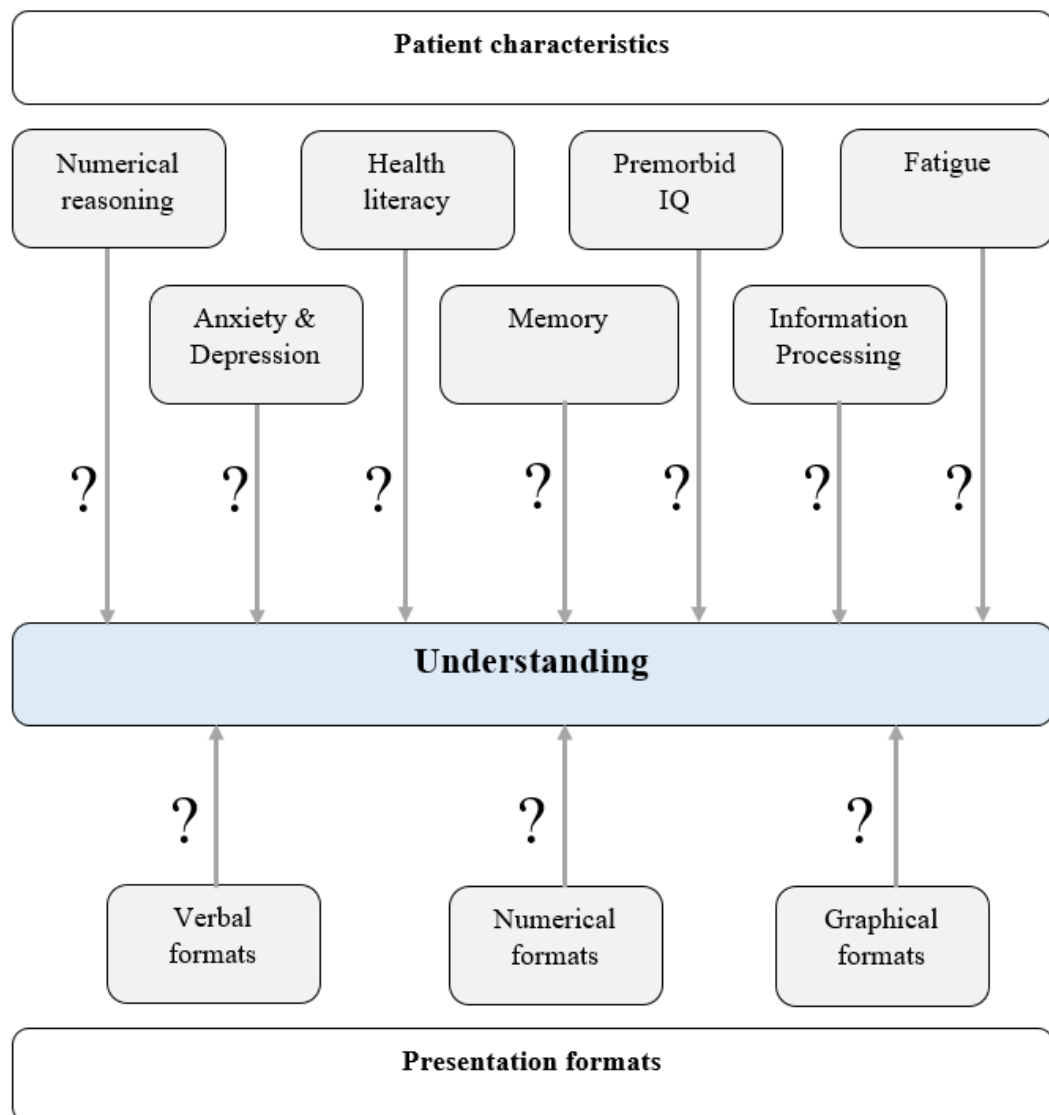


Figure 4.1 Theoretical framework 1: Factors affecting MS patients' understanding of treatment risks and benefits

Key: Grey arrows, no relationship; Question, Untested factors; arrows do not signify causation

4.2 Experiment 1 methodology

4.2.1 Participants

A total of 45 patients diagnosed with the relapsing-remitting form of Multiple Sclerosis (RRMS) under the current diagnostic criteria (Polman et al., 2011) were included in this experiment. Patients were recruited from two hospitals in the UK: King's

College Hospital NHS Foundation Trust and Queen Elizabeth Hospital as part of the Lewisham and Greenwich NHS Trust. The experiment received ethical approval from the Psychology Department Ethics Committee at Royal Holloway and the NHS Research Ethics Committee (see appendix 3 and 4).

Patients were eligible to take part in the experiment if currently taking a DMD, able to provide informed consent and meet task demands of the experiment in terms of sensorimotor abilities. People with any significant changes in the condition or medication in the last 4 weeks were excluded. The exclusion criteria also extended to patients with significant medical or psychiatric condition other than MS. All patients were initially assessed on a visual acuity scale, also known as a Jaeger chart (Keeney & Duerson, 1958), given that visual impairments are a commonly occurring symptom in MS. Patients were excluded if visual acuity was less than 20/70.

4.2.2 Materials and design

Hypothetical medical information was used throughout the experiment to ensure sensitive medical information was not provided to patients in the absence of healthcare professionals and appropriate support.

Patients in the current experiment received information about two hypothetical diseases. A brief summary of the disease was initially provided followed by a list of symptoms (see appendix 12 for example of one disease). To mimic the progressive and uncertain nature of MS, patients were informed that the hypothetical diseases were progressive but that the rate of progression could vary between patients. It was also stated that individuals may not experience all symptoms of the disease. For each disease, patients also received information about the minor risks, adverse risks and benefits for two hypothetical treatments. Specifically, each hypothetical treatment presented four minor risks, two adverse risks and two benefits (i.e. each treatment had eight outcomes). The diseases and the treatments names were designed by the experimenter to increase

validity. All names were checked for their similarity with names of real diseases and treatments in a small survey with a non-clinical population group, prior to conducting the experiment (N=10). Each of the minor risks and adverse risks assigned to the treatments in this experiment were plausible and could be associated with real medications, further increasing validity. Prior to selecting these risks, a comprehensive list of treatment risks were checked by a small non-clinical population group (N=10). Risks were selected and assigned as either minor or adverse risks if 80% of the survey sample were in agreement about the level of risk. With respect to treatment benefits, these related back to the symptoms of the hypothetical disease; i.e. the benefit of the treatment was a delay in progression of a symptoms of the disease. Even though treatments were hypothetical, the risk-benefit profiles were drawn from real clinical trials of DMDs (e.g. Cohen et al., 2010; IFNB Multiple Sclerosis Group, 1993; Kappos et al., 2010; Miller et al., 2009; O'Connor et al., 2009). That is, for each disease, one treatment represented a second-line treatment (i.e. high risk and high benefit) whereas the other treatment had a low risk-benefit profile. To ensure the adverse risks of DMDs could be clearly represented, a denominator of 1000 patients were chosen and presented with all formats and during all comprehension questions (i.e. treatment outcome out of 1000 patients). Moreover, all minor risks, adverse risks and benefits of the treatments were provided for multiple time points (i.e. after 1 year, 2 years and 5 years of taking the treatment) in order to mimic the long-term effects of taking DMDs in MS.

The formats to present treatment risks (minor and adverse) and benefits were manipulated in the present experiment. Verbal terms, based on EC guidelines, were employed to represent numerical information (EC Guidelines, 2009; see table 4.1 for example). The two numerical formats used to present treatment information consisted of frequencies and percentages. Several graphical formats were also employed in the present experiment, comprising: tables, bar charts, line graphs, pie charts and pictographs.

Finally, graphical format elements were also manipulated in the present experiment, including: pictograph figures (abstract or human), pictograph arrangement (consecutive or random), bar chart orientation (vertical or horizontal) and the addition of numbers with some graphical formats (graphical formats with numbers and without numbers). All formats were developed by authors. Tables, bar charts, line graphs and pie charts were designed in Microsoft Excel, and pictographs were designed using an available online template ("Icon array", n.d.) (see figure 4.2 for some examples of author-developed formats).

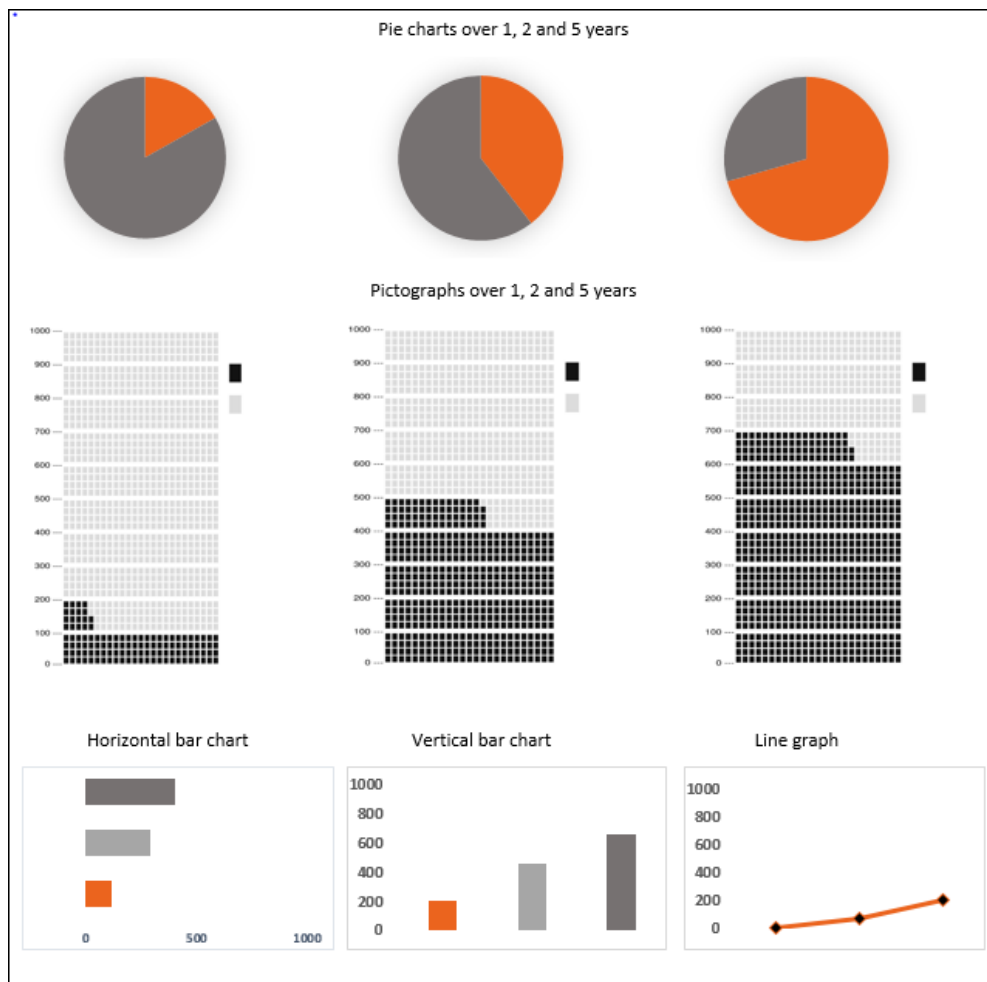


Figure 4.2 Examples of graphical formats presented in Experiment 1

A within-subjects design was employed in the present experiment, so that every patient received information about all treatment minor risks, adverse risks and benefits presented in all possible formats across both diseases. In total, patients were presented with 16 different formats. Each format was employed twice in immediate succession. Thus, 16 different formats were used to present 32 treatment outcomes (see tables 4.3 and 4.4; see appendix 13 for presentation formats presented with Treatment A only). To dissipate order effects, the initial order of all formats and treatment outcomes were randomised using a random number generator (see tables 4.3 and 4.4). In addition, the order in which the hypothetical diseases and treatments were presented to each patient was counterbalanced between patients using a Latin square design (Bradley, 1958; Winer, 1962) (see table 4.5).

The main outcome measures in the experiment were understanding of treatment information and decisional conflict for treatment choice. In addition, the following patient characteristics were assessed: demographics, numerical reasoning, health literacy, premorbid IQ and symptoms of MS (i.e. fatigue, affective and cognitive symptoms).

Table 4.3 Randomisation order of treatment outcomes and formats for hypothetical disease 1

Medical disease	Treatment	Treatment outcome	Formats
Disease 1 (<i>Septhitus</i>)	Treatment A (<i>Difoxitin</i>)	Adverse risk	Vertical bar chart, with numbers
		Benefit	Vertical bar chart, with numbers
		Adverse risk	Line graph, with numbers
		Minor risk	Line graph, with numbers
		Minor risk	Pie chart
		Minor risk	Pie chart
		Minor risk	Horizontal bar chart
		Benefit	Horizontal bar chart
Disease 1 (<i>Septhitus</i>)	Treatment B (<i>Tephemerol</i>)	Minor risk	Consecutive pictograph, abstract figures
		Adverse risk	Consecutive pictograph, abstract figures
		Benefit	Line graph
		Minor risk	Line graph
		Minor risk	Vertical bar chart
		Minor risk	Vertical bar chart
		Benefit	Pie chart, with numbers
		Adverse risk	Pie chart, with numbers

Names assigned to hypothetical medical disease and hypothetical treatments provided in brackets; all formats were presented twice in immediate succession; formats provided with treatment A are included in appendix 13

Table 4.4 Randomisation order of treatment outcomes and formats for hypothetical disease 2

Medical disease	Treatment	Treatment outcome	Formats
Disease 2 (<i>Pariplexia</i>)	Treatment C (<i>Tripoxac</i>)	Minor risk	Horizontal bar chart, with numbers
		Adverse risk	Horizontal bar chart, with numbers
		Minor risk	Random pictograph, abstract figures
		Benefit	Random pictograph, abstract figures
		Minor risk	Random pictograph, human figures
		Minor risk	Random pictograph, human figures
		Benefit	Percentages
		Adverse risk	Percentages
Disease 2 (<i>Pariplexia</i>)	Treatment D (<i>Lapoxil</i>)	Adverse risk	Consecutive pictograph, human figures
		Benefit	Consecutive pictograph, human figures
		Minor risk	Verbal format
		Minor risk	Verbal format
		Adverse risk	Table
		Minor risk	Table
		Benefit	Frequencies
		Minor risk	Frequencies

Names assigned to hypothetical medical disease and hypothetical treatments provided in brackets; all formats were presented twice in immediate succession

Table 4.5 Latin square design for Experiment 1

Disease	Treatment	Treatment	Disease	Treatment	Treatment
1	A	B	2	C	D
1	B	A	2	D	C
2	C	D	1	A	B
2	D	C	1	B	A

4.2.2.1 Patient understanding

Understanding of treatment risk and benefit information was assessed by asking patients three comprehension questions immediately after presenting information in a particular format, reflecting the three time points (i.e. 1 year/2 years/5 years). For instance, after presenting each treatment outcome patients were asked: ‘Out of 1000 people, how many people would experience this minor risk/adverse risk/benefit after 1 year/2 years/5 years?’ (see appendix 13 for example of comprehension questions). Questions were author-developed for the purpose of the current experiment, but were adapted from previous studies (Hamstra et al., 2014; Hawley et al., 2008). Answers were marked as correct and awarded 1 point if patients either stated the precise value or provided an answer within a range of + or – 10. Answers within a 1% range of the total denominator (i.e. + or - 10 for 1000 patients) were accepted due to the difficulty in reporting the most precise numbers when these were not presented with some formats. In fact, 100% on scores is not generally considered a sensitive nor required measure to measure understanding and it is practical for responses that indicate understanding to be scored accordingly (Tait et al., 2010). Similar cut-offs for acceptable correct answers for comprehension questions have also been applied in previous studies (Hamstra et al., 2014; Hawley et al., 2008; McCaffery et al., 2012). Incorrect or missing answers were scored as 0. The maximum correct answers for treatment side-effect, risks or benefits was three points. Given that each format presented information about two treatment outcomes, the maximum score for each format was six points.

4.2.2.2 Decisional conflict

Following the presentation of two hypothetical treatments for each disease, patients were required to make a treatment decision or choose to take no treatment. Following a treatment decision, the DCS was employed to assess patients’ conflict in their treatment decisions (O’Connor, 1995). In the present experiment, the DCS was

given twice to each patient. The DCS was provided after disease 1 (for treatments A and B) and disease 2 (for treatments C and D).

The DCS is a multi-dimensional scale of 16 items divided into 5 subscales: personal uncertainty (3 items) and its modifiable deficits of feeling uninformed (3 items), unclear values (3 items), inadequate support (3 item), and perception that an ineffective choice has been made (4 items). Participants' ratings on these subscales correspond to the treatment choice they make at the start of the scale, which includes the option of being unsure. The scores can be standardised to range from 0 (no decisional conflict) to 100 points (extreme decisional conflict) (O'Connor, 1995). Scores of 25 are associated with continuing with a decision, whereas scores that exceed 38 are associated with delay in decision-making. The DCS has been shown to have high reliability, with test-retest correlation of 0.81. Internal consistency for the total DCS score ranged from 0.78 to 0.92, and this ranged from 0.58 to 0.92 for the DCS subscales (O'Connor, 1995). The scale has also been demonstrated as a valid measure to discriminate between patients who accept or reject the decision, relative to patients who delay the decision (O'Connor, 1995).

4.2.2.3 Patient characteristics

In addition to the main outcome measures, patients in the experiment were also assessed on: numerical reasoning, health literacy, anxiety, depression, fatigue, premorbid IQ and cognitive abilities. Patient demographics were also recorded.

Demographics

Patient demographic information recorded as part of the experiment includes: age, gender, level of education, employment status, years since MS diagnosis and current DMD. All demographic information was collected by questioning patients at the start of the experiment.

Patients' disability status was also recorded in the present experiment by using the Hauser Ambulation Index (Hauser et al., 1983). Participants were timed while walking 25 feet and their walking ability was graded on a 7-point Likert scale, with 0 referring to asymptomatic patients and higher scores indicating severe disability.

Health Literacy

The present experiment employed the Rapid Estimate of Adult Literacy in Medicine - Revised task (REALM-R; Bass, Wilson, & Griffith, 2003) which is a short 8-item word recognition task designed to rapidly assess patients for health literacy problems. The shortlisted words of REALM-R have been chosen from 66 words used in the original Rapid Estimate of Adult Literacy task (REALM), and demonstrates very high internal consistency. The task shows a correlation of 0.72 with the REALM test and 0.64 with other commonly used health literacy tasks (Bass et al., 2003).

This task was chosen due to its quick administration length to keep the experiment duration short and avoid patient fatigue. The task required participants to verbally read aloud a list of 11 health related words, with correct pronunciation of words marked as a correct response. The three initial words in the list were not scored but are usually included to decrease test anxiety in patients. Therefore, the maximum score on this measure was eight, with scores of six or below indicating low health literacy.

Numerical reasoning

Numerical reasoning and skills were assessed using the series completion subtask from the Verbal and Spatial Reasoning Task (VESPAR; Langdon & Warrington, 1995). The series completion task consisted of 25 items, progressively increasing in difficulty from simple arithmetic series to more complex numerical patterns. Participants were required to select the subsequent number to complete a series (i.e. 2, 4, 8, ?) from a choice of four numbers (16, 10, 12, 20). The two "screen" items at the beginning of the

task had to be answered correctly before attempting the test items. Scores were classified as low numerical reasoning if 2 standard deviations below the control mean (Langdon & Warrington, 1995).

Depression and anxiety

Affective MS symptoms were assessed using the Hospital Anxiety and Depression Scale in the current experiment (HADS; Zigmond & Snaith, 1983). The HADS measure is often used in non-psychiatric settings, usually taking about 2-6 minutes to complete. The scale comprises a subscale for depression and a subscale for anxiety, each containing 7 items in total, with 4-point verbal rating scales for each item (i.e. a score of 0 to 3). The maximum points for each subscale is 21 points. Patients scoring above 11 points on each of the subscales are considered to have depression or anxiety. Scores between 8 and 10 on each subscale indicates that patients have borderline depression or anxiety, with scores below 8 referring to no affective symptoms in MS patients.

Reviews on the HADS measure have demonstrated high internal consistency for both subscales, with Cronbach's alpha ranging from 0.67 to 0.93. Reviews have also supported its two-factor structure, test-retest reliability, and construct validity (Bjelland, Dahl, Haug, & Neckelmann, 2002; Herrmann, 1997). HADS also demonstrates sensitivity of 90% and specificity of over 87% when conducted with MS patients (Honarmand & Feinstein, 2009). In fact, the HADS anxiety subscale has recently been recommended for use in MS patients (Litster et al., 2016), further supporting its use in the current experiment.

Fatigue

The Fatigue Severity Scale (FSS), originally developed for people with MS, was administered in the present experiment to identify patients with significant fatigue

(Krupp, Alvarez, LaRocca & Steinberg, 1989). Compared to other scales of fatigue, FSS was found to be highly discriminative and a reliable measure of fatigue (Flachenecker et al., 2002). The FSS consists of a seven-point scale for nine items and requires patients to rate their experience of physical or psychological fatigue in the past seven days. The test takes between 2-5 minutes to administer. After averaging scores on all items, patients scoring 5 or higher were deemed to have severe fatigue, consistent with classifications in previous studies that have employed this scale (Bakshi et al., 2000; Flachenecker et al., 2002; Lerdal, Celius, Krupp, & Dahl, 2007).

Premorbid IQ

Measures of premorbid intellectual function (IQ) aims to quantify the cognitive impact of neurological injury by using assessments that are resistant to neurological damage, typically measuring crystallised intelligence or stored knowledge (Green et al., 2008). The Wechsler Test of Adult Reading is one such measure (WTAR; Wechsler, 2001), developed and normed alongside the Wechsler Adult Intelligence Scale (Wechsler, Laicardi, & Orsini, 1997). WTAR is shown to be a highly stable test which does not appear to be altered by the cognitive effects of different types of brain injury or impairments, such as those present in MS (Green et al., 2008). The measure itself is an untimed word-pronunciation task which requires respondents to read aloud 50 irregular English words. All words pronounced correctly were scored with 1 point. Thus, patients could score a maximum of 50 points on this task. To classify patients with poor IQ, raw scores were converted to standard scores according to the age-norms and then converted to scaled scores as per the testing manual (Wechsler, 2001). Scores below 85 standard scores (<1 SD) were classified as poor IQ.

Cognitive impairment

The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS; Langdon et al., 2012) was employed as a screening tool to identify cognitive deficits of

information processing speed, verbal memory and visual memory. Although cognitive impairments in MS are not exclusive to these domains, these abilities are the most likely to be affected in MS (Langdon et al., 2012). The subtests included as part of this battery were: the Symbol Digit Modalities Test (SDMT; Smith, 1982), the California Verbal Learning Test-II recall trials (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) and the Brief Visuospatial Memory Test Revised, recall trials (BVMTR; Benedict, 1997) administered in this order as recommended by the authors. To classify whether MS patients were impaired on any of these measures, patients scoring 1.5 standard deviation below the control mean were considered as cognitively impaired according to a UK validation of BICAMS (Orchard, Giovannoni & Langdon, 2013).

The SDMT task consists of abstract symbols, randomly paired with single digits as a key on top of the page. This is then followed by randomly arranged symbols alone on the rest of the page. The respondent's task is to orally state the digit corresponding to the abstract symbols according to this key. Participants are required to complete 10 example items prior to commencing the actual task for 90 seconds. The SDMT measure is shown to have high sensitivity of up to 90% in detecting cognitive impairment in MS relative to similar tasks (Parmenter, Weinstock-guttman, Garg, Munschauer, & Benedict, 2007; Sepulcre et al., 2006; Strober et al., 2009; Van Schependom et al., 2014), even at one year follow-up (López-Góngora, Querol, & Escartín, 2015).

The CVLT-II is a simple immediate list recall task, where participants are given five trials to one item list. The list consists of 16 words, with four items belonging to four different categories but arranged in a random order and is read aloud five times at a slightly slower rate than 1 second or less (Langdon et al., 2012). It has been noted that low scores on the CVLT-II list recall task predicts poor understanding of the informed consent procedure in MS (Basso et al., 2010) and is considered a sensitive measure to

detect cognitive impairment in MS, also demonstrating high external validity (Stegen et al., 2010).

The BVMTR is a visuospatial memory task consisting of an array of six figures presented three times to participants for 10 seconds each. Once the array is removed, participants are required to draw the figures from memory, ensuring that the correct shapes are drawn in the correct location. Figures are scored for their correct shape and their correct location, and patients could score a maximum of 12 points in each trial. The total score is calculated by summing the scores of all three trials. The BVMTR is considered a reliable measure for MS patients; scores on this task are significantly correlated with total brain lesions in MS (Benedict et al., 2002) and also shows high sensitivity in detecting cognitive impairments in MS (Strober et al., 2009).

4.2.3 Procedure

MS patients were first assessed for eligibility by the Consultant Neurologist or the MS Specialist Nurse at the two hospital clinics. Interested patients were then invited to take part in the experiment and were presented with a NHS approved information sheet and consent form (see appendix 14). Following consent, an appointment was made with patients to take part in the experiment. The experiment was conducted either at the clinics or at the patient's home, depending on patient's preference. The experiment took approximately 2 hours to complete and was conducted face-to-face using offline materials only.

Initially, patients were presented with the visual acuity scale to ensure they were eligible to view the remaining experiment (see section 4.2.1). If eligible to continue, patients were asked demographic questions and assessed on the disability status scale. Next, patient characteristics were measured in the following order: health literacy, numerical reasoning, depression and anxiety, fatigue and premorbid IQ. Patients were then provided with two hypothetical diseases, each of which were followed by two

hypothetical treatments presented in different formats. A 2-minute break was provided after the first disease but patients were encouraged to take more breaks when necessary. Comprehension questions to assess understanding were provided after each treatment outcome. Patients were also required to make their treatment decision and complete the DCS measure at the end of each disease (i.e. after viewing two hypothetical treatments). Finally, the BICAMS measure was conducted with patients. All patients were then debriefed and informal consent was obtained to confirm whether patients would like to be contacted again for additional studies in this thesis project.

4.2.4 Sample size

Sample size estimates were based on power calculations to detect a medium effect (0.5) on MS patients' understanding scores. A previous questionnaire that assessed understanding in MS patients found a large effect size in detecting patients with good understanding and poor understanding of their condition. However, only 5 out of 19 items focused on patients' understanding of MS treatments (Heesen et al., 2015; Köpke et al., 2014). We therefore chose a conservative medium effect size for this experiment. It was estimated that for an alpha of 0.05 and power of 0.80, a minimum number of 45 MS patients were required to take part in the experiment.

4.2.5 Statistical analysis

All statistical analyses were carried out using SPSS 21. Means and standard deviations were provided for all continuous data. Maximum scores were also presented for all measures in the experiment. A test of normality was conducted for the understanding outcome measure for each format using the Shapiro-Wilks test. The assumption of normality was significantly violated for each format ($p < .001$) and therefore a nonparametric Friedman analysis of variance was conducted. Where the Friedman test was significant, pairwise comparisons were conducted by using the nonparametric Wilcoxon Signed Ranks test. Bonferroni corrections were applied for multiple

comparisons. Effect sizes are calculated for all pairwise comparisons by dividing the z score by the square root of total number of observations, based on Rosenthal's formula (Rosenthal, 1994); where, 0.1, 0.3 and 0.5 equates to small, medium and large effect sizes, respectively. For the purpose of the analysis, several formats were sometimes collapsed into one average understanding score.

In addition, two bivariate Pearson's product moment correlations were conducted to assess the relationship between patient understanding and the standardised scores of the decisional conflict scale, including all subscales. This is because all patients were exposed to both hypothetical diseases, and thus made two treatment decisions in total (i.e. treatment decision for disease 1 and treatment decision for disease 2; see tables 4.3 and 4.4). Analysis with standardised rather than raw DCS scores have been recommended by the authors of the DCS (O'Connor, 1995). Bivariate Pearson's product-moment correlations were also computed to assess the relationship between understanding and raw scores on measures of numerical reasoning, health literacy, premorbid IQ and symptoms of MS. Due to multiple correlations, a stringent alpha of $p < .01$ was applied and accepted as significant.

4.3 Results

4.3.1 Patient demographics

Analysis was conducted for all 45 patients in the current experiment. Patient demographic information is displayed in Table 4.6.

Table 4.6 Patient demographics and disease status for Experiment 1 (n=45)

	Mean (SD)	n (%)
Age, years	42.51 (9.46)	
Gender		
Female		34 (75.6)
Male		11 (24.4)
Level of education		
High school		13 (28.9)
College		7 (15.6)
Bachelor's degree		15 (33.3)
Postgraduate		10 (22.2)
Employment status		
Full-time (>16 hours)		17 (37.8)
Part-time (<16 hours)		8 (17.8)
Self-employed		6 (13.3)
Unemployed		9 (20.0)
Medical leave		5 (11.1)
Retired		0 (0)
Time since MS diagnosis, years	9.80 (8.10)	
HAI disability scale	1.49 (1.67)	
Current DMD		
Interferon betas		18 (40)
Glatiramer Acetate		4 (8.9)
Teriflunomide		0 (0)
Fingolimod		6 (13.3)
Alemtuzumab		0 (0)
Dimethyl Fumarate		9 (20)
Natalizumab		7 (15.6)
Mitoxantrone		1 (2.2)

DMD= disease-modifying drugs; HAI = Hauser Ambulation Index

* Score of 1 on HAI scale = Able to walk normally but report fatigue interfering with athletic activities

4.3.2 The effect of verbal and numerical formats on patients' understanding

There was a statistically significant difference between verbal and numerical formats (verbal, percentages and frequencies), $X^2(2) = 74.112$, $p < .001$. Pairwise comparisons were conducted to statistically compare the means for verbal terms ($M=.04$, $SD=.21$), percentages ($M=4.69$, $SD=2.17$) and frequencies ($M=5.82$, $SD=.91$). Pairwise comparisons revealed that understanding was greater for frequencies compared to verbal terms ($z=-6.386$, $r=0.67$, $p < .001$) and percentages ($z=-3.308$, $r=0.35$, $p < .01$). Understanding was also greater for percentages compared to verbal terms ($z=-5.769$, $r=0.61$, $p < .001$).

4.3.3 The effect of graphical formats without numbers displayed on patients' understanding

There was a statistically significant difference between graphical formats that did not display numbers (bar charts, pictographs, line graph and pie chart) on patients' understanding of treatments, $X^2(2) = 92.779$, $p < .001$. Pairwise comparisons were conducted to statistically compare the means for bar charts ($M=4.11$, $SD=1.24$), pictographs ($M=2.56$, $SD=.85$), line graphs ($M=3.71$, $SD=1.53$) and pie charts ($M=1.09$, $SD=.95$). Understanding was greater for bar charts compared to pictographs ($z=-5.407$, $r=0.57$, $p < .001$) and pie charts ($z=-5.772$, $r=0.61$, $p < .001$). Understanding was also greater for line graphs compared to pictographs ($z=-4.359$, $r=0.46$, $p < .001$) and pie charts ($z=-5.809$, $r=0.61$, $p < .001$). Understanding was also greater for pictographs compared to pie charts ($z=-5.558$, $r=0.59$, $p < .001$). There was no significant difference in patients' understanding for information presented in bar charts and line graphs ($p=.088$).

4.3.4 The effect of graphical formats with numbers displayed on patients' understanding

There was no statistically significant difference between graphical formats that displayed numbers (tables, bar chart, line graph and pie chart) on patients' understanding, $X^2(3) = 3.194$, $p=.363$.

4.3.5 The effect of numbers on graphical formats on patients' understanding

There was a statistically significant difference between graphical formats that displayed numbers and the corresponding graphical formats without numbers on patients' understanding of treatments, $X^2(1) = 45.000$, $p < .001$. According to the mean scores, understanding was greater for graphical formats with numbers displayed ($M=5.87$, $SD=.66$) compared to graphical formats without numbers displayed ($M=3.26$, $SD=.99$). Further pairwise comparison revealed that pie charts showed the greatest effect when numbers were displayed compared to no numbers ($z=-5.915$, $r=0.62$, $p < .001$). The effects for other formats were as follows: bar chart horizontal ($z=-4.763$, $r=0.50$, $p < .001$), bar chart vertical ($z=-5.424$, $r=0.57$, $p < .001$) and line graph ($z=-5.341$, $r=0.56$, $p < .001$).

4.3.6 The effect of bar chart orientation on patients' understanding

There was a statistically significant difference between orientation of bar charts (horizontal bar charts, vertical bar charts) on patients' understanding, $X^2(1) = 12.902$, $p = .001$. According to the mean scores, understanding was greater for bar charts with horizontal orientation ($M=5.20$, $SD=1.01$) compared to bar charts with vertical orientation ($M=4.77$, $SD=.95$, $z=-3.441$, $r=0.36$).

4.3.7 The effect of pictograph figures on patients' understanding

There was no statistically significant difference for the figures displayed in pictographs (human figures, abstract figures) on patients' understanding, $X^2(1) = .231$, $p = .631$.

4.3.8 The effect of pictograph arrangement on patients' understanding

There was a statistically significant difference in arrangement of pictographs (consecutive arrangement, random arrangement) on patients' understanding, $X^2(1) = 45.000$, $p < .001$. According to mean scores, understanding was greater for consecutive arrangement ($M=4.26$, $SD=1.38$) compared to random arrangement ($M=.86$, $SD=.61$, $z=-5.856$, $r=0.62$).

4.3.9 Patient understanding and decisional conflict

A bivariate Pearson product-moment correlation conducted for the understanding and decisional conflict score for hypothetical disease 1 revealed no significant correlation between patients' understanding and the total DCS measure. There were also no significant correlations between understanding and the subscales of the DCS measure (see table 4.7).

Similarly, a bivariate Pearson product-moment correlation conducted for the understanding and decisional conflict score for hypothetical disease 2 revealed no significant correlation between patients' understanding and the total DCS measure. There were also no significant correlations between understanding and the subscales of the DCS measure (see table 4.8).

Table 4.7 Correlations between patient understanding and decisional conflict scores for hypothetical disease 1

	Max score	Mean	SD	Correlation
Total understanding	48	38.84	6.03	
DCS informed	100	14.44	14.80	-.130
DCS values	100	19.62	17.78	-.246
DCS support	100	21.48	17.09	-.068
DCS uncertainty	100	42.40	24.54	.033
DCS effective	100	46.30	61.28	-.093
DCS total score	100	24.57	14.41	-.122

* = indicates significance at the $p < .05$ level; ** at $p < .01$ level; *** at $p < .001$ level; DCS, Decisional Conflict Score

Table 4.8 Correlations between patient understanding and decisional conflict scores for hypothetical disease 2

	Max score	Mean	SD	Correlation
Total understanding	48	28.31	5.50	
DCS informed	100	19.83	26.89	-.195
DCS values	100	19.25	18.10	-.237
DCS support	100	23.51	19.49	-.100
DCS uncertainty	100	41.37	24.38	.062
DCS effective	100	43.89	26.73	.110
DCS total score	100	27.12	15.39	-.057

* = indicates significance at the $p < .05$ level; ** at $p < .01$ level; *** at $p < .001$ level; DCS, Decisional Conflict Score

4.3.10 Patient understanding and patient characteristics

Patients were assessed for numerical reasoning skills, health literacy, premorbid IQ and MS symptoms in the current experiment. As shown in table 4.9, MS patients in this experiment mostly showed symptoms of anxiety, fatigue and cognitive impairments. A bivariate Pearson product-moment correlation coefficient revealed significant correlations for patients' health literacy ($r = .713$, $p < .01$), numerical reasoning ($r = .609$, $p < .01$), premorbid IQ ($r = .641$, $p < .01$), information processing speed ($r = .473$, $p < .01$) and verbal memory ($r = .477$, $p < .01$). Means, standard deviations and correlations for all factors are presented in table 4.10.

Table 4.9 Patients impaired on assessments of numerical reasoning, health literacy, premorbid IQ and MS symptoms (n=45)

Patient characteristics and MS symptoms	n (%)
Health literacy	3 (6.7)
Numerical reasoning	4 (8.9)
Depression	6 (13.3)
Anxiety	14 (31.1)
Fatigue	21 (46.7)
Premorbid IQ	1 (2.2)
Information processing speed	13 (28.9)
Verbal memory	15 (33.3)
Visual memory	25 (55.6)

Table 4.10 Correlations between patient understanding and patient characteristics

Patient characteristics	Max score	Mean	SD	Correlation
Total understanding	96	63.16	10.89	
Numerical reasoning	25	16.20	3.61	.609**
Health literacy	8	7.49	1.25	.713**
Depression	21	5.02	4.23	-.194
Anxiety	21	7.51	4.57	-.250
Fatigue	63	42.64	13.56	-.202
Premorbid IQ	50	37.78	6.86	.641**
Information processing speed	110	57.07	11.09	.473**
Verbal memory	80	48.44	14.08	.477**
Visual memory	36	20.29	6.99	.288

* = indicates significance at the $p < .05$ level; ** at $p < .01$ level; *** at $p < .001$ level, correlations in bold accepted as significant due to multiple correlations

4.4 Discussion

In order to make informed treatment decisions, it is important that MS patients are able to understand the risks and benefits of treatments (see section 1.3). Studies with

both non-clinical and clinical population groups have shown that the formats used to present treatment risk and benefit information can affect understanding. However, findings conducted with MS patients are very limited. The present experiment was the first to conduct a comprehensive assessment of several presentation formats with MS patients in order to examine which presentation formats could maximise understanding of treatment information.

Guidelines made by EC recommend the use of standardised verbal terms to present treatment risks and benefits to patients (EC Guidelines, 2009). These terms are currently employed within the UK National Healthcare Service (NHS) to present DMD risks and benefits to patients with MS (see appendix 11). However, the present experiment found that MS patients cannot effectively understand treatment risks and benefits when verbal formats were presented alone in comparison to information presented in numerical formats. This is consistent with previous studies that have been conducted with both non-clinical and clinical patient groups (Berry et al., 2003; Berry et al., 2002; Knapp et al., 2009). It has been suggested that verbal formats should be provided together with numerical formats to maximise understanding (Lipkus, 2007). This was not explored in the present experiment. However, previous studies have shown no improvements in understanding when information was presented both verbally and numerically (Knapp et al., 2015), indicating that verbal formats are likely to interfere with understanding of numerical information.

Although numerical formats can improve understanding in comparison to verbal formats, it is also important to identify whether different types of numerical formats affect MS patients' understanding. It was predicted that there will be no differences in understanding when numerical information was presented in either frequencies or percentages, due to the inconsistent findings in the literature. However, this hypothesis was not supported. Significant differences in understanding of treatments was observed in

the current experiment when presented in frequencies and percentages, in favour of frequencies. Although this result supports only some previous findings (Gigerenzer, 1996; Gigerenzer & Edwards, 2003; Hoffrage & Gigerenzer, 1998), these findings are based on a complex screening test problem rather than information about treatment risks and benefits. The current results did not support previous studies that have assessed numerical formats in the context of treatment information specifically (Waters et al., 2006; Woolshin & Schwartz, 2011). However, these studies were conducted with a general population who are unlikely to make decisions based on treatment risk and benefit information.

Moving onto graphical formats, it was hypothesised that pictographs would maximise understanding of treatment information in MS patients, considering that several studies with non-clinical and clinical populations favour the use of pictographs relative to other graphical formats to improve understanding (Hamstra et al., 2014; Hawley et al., 2008; McCaffery et al., 2012; Schapira et al., 2001; Schapira et al., 2006). Nevertheless, this hypothesis was not supported in the present experiment. Understanding of treatment information was greatest when patients were presented risks and benefits using bar charts and line graphs. This is consistent with some previous findings which show support for bar charts (Brewer et al., 2012; Hamstra et al., 2014; Hawley et al., 2008). Furthermore, the least understood graphical format was pie charts followed by pictographs in the current experiment, indicating that these formats should generally be avoided when presenting treatment information to MS patients. Although inconsistent with findings from previous studies, one reason for the results of the present experiment may be due to the long-term treatment risks and benefits that were presented to MS patients in order to mimic DMD risk and benefit profiles. Bar charts and line graphs are both able to display long-term trends for treatment outcomes in one graph, whereas equivalent long-term risks and benefits for pie charts or pictographs can only be presented using multiple charts.

Given that decisions about DMDs are generally based on treatment risks and benefits over a longer period of time, the present experiment signifies that long-term DMD risk-benefit profiles could be easier to interpret when presented using a bar chart and line graph format.

Several elements of graphical formats were also manipulated in the current experiment. Following recommendations that understanding of treatments can be improved if numbers are added to graphs (Bunge et al., 2010; Lipkus, 2007), the current experiment added numbers to bar charts, line graphs and pie charts and also added numbers to tables. As hypothesised, understanding of treatment risks and benefits was improved when numbers, in the form of frequencies, were presented alongside graphical formats.

Orientation of graphical formats was also manipulated in the present experiment. In contrast to previous findings, orientation did affect how MS patients' understood the risks and benefit of treatments. Specifically, horizontally displayed information showed better understanding than verbal formats, consistent with one previous study (Price et al., 2007). Explanations for better understanding of horizontal formats has not been previously discussed in the literature. One possible reason could be that horizontally displayed information is able to effectively present trends of treatment risks and benefits over time in comparison to graphs presented vertically. Note, however, that only orientation of bar charts was manipulated in the present experiment. It is therefore not possible to make any reliable conclusions about the effects of orientation for different graphical formats.

The presentation styles of pictographs were further manipulated in the current experiment. As predicted, consecutively arranged pictographs significantly improved accuracy of treatment understanding when compared to pictographs that were randomly arranged. This is consistent with previous studies conducted with non-clinical populations

(Schapira et al., 2006; Schapira et al., 2001). However, the result of the present experiment differs to the only other study conducted with MS patients which showed no improvements in understanding information about treatment benefits when pictographs were consecutively arranged versus pictographs arranged randomly (Kasper et al., 2011). The findings were different despite the present experiment sharing similar features with the study by Kasper and colleagues (2011), such as employing only hypothetical treatment information and displaying the pictograph in a total of 1000 figures. To note, Kasper and colleagues (2011) did find that MS patients' understanding of treatment risks specifically was better when presented using the consecutive arranged pictograph. Since the current experiment did not explore understanding individually for treatment minor risks, adverse risks or benefits, it was not possible to replicate these effects. With regards to the figures displayed within pictographs, the present experiment found no evidence of the impact of figures on understanding. Thus, despite human-figures being commonly employed in pictographs (Henneman et al., 2013), this is not an essential requirement when presenting treatments using pictographs as only the arrangement of figures can affect understanding in MS patients.

Associations between understanding of treatment information and the conflict patients experience for treatment decisions was also examined in the present experiment. It was predicted that improving understanding could reduce MS patients' decisional conflict. However, this hypothesis was not supported. This is inconsistent with the very few studies that have directly evaluated the relationship between understanding and decisional conflict (Cormiers et al., 2015; Sun, 2005). The differences between these findings and those of the current experiment could be because MS patients' understanding was measured for a range of different presentation formats in the current task. Moreover, since the DCS measure tends to assess several different components that contribute to decisional conflict, all these factors may not be correlated with patient

understanding. For this reason, correlations were also conducted between understanding scores and the different DCS subscales in the current experiment. Yet, there were no correlations for understanding with any of the DCS subscales. Importantly, there was no correlation between understanding scores and the DCS informed subscale, which typically assesses understanding of alternate treatment options. The absence of this relationship could be because the informed DCS subscale tends to only measure perceived knowledge, which may not necessarily relate to subjective understanding of information (O'Connor, 1995; Stacey et al., 2014). Thus, according to the current experiment improving patients' understanding did not reliably reduce MS patients' conflict for treatment decisions.

The relationship between understanding and patient characteristics were also examined in this experiment. As predicted, patients' numerical reasoning skills were positively related with patients' understanding. In other words, patients with low numeracy skills were more susceptible to misunderstanding treatment information when presented in different formats. Similar effects have been found in previous studies (e.g., Hamstra et al., 2014; Paling, 2003; Peters et al., 2011). Understanding was also strongly related with health literacy and premorbid IQ in the current experiment. Given that health literacy, numeracy and IQ can relate to patients' educational background (Peters, 2008), the current finding indicates that patients with low educational background may be more susceptible to misunderstanding treatment information. The current experiment also assessed the relationship between MS symptoms and patient understanding. Cognitive impairments, particularly information processing speed and verbal memory were significantly correlated with patient understanding. However, anxiety, depression and fatigue showed no significant relationship with MS patients' understanding. This indicates that patients presenting with cognitive impairments may be more susceptible to poor understanding of treatment risks and benefits, compared to patients displaying other

symptoms of MS. To note, however, it is also likely that the current experiment did not have enough statistical power to detect the relationship between other patient symptoms which may be identified in future studies with better statistical power. Yet, this does emphasise that all significant correlations in the current experiment had large effect sizes than all other nonsignificant correlations.

The current experiment also has a number of limitations which must be addressed prior to drawing any conclusions. First, several other formats to present treatment risks and benefits were not assessed in this experiment. For instance, although frequencies were shown to improve understanding of treatment information relative to percentages, frequencies can also be presented in different ratios; either by keeping the numerator constant (1-in-X format) or by keeping the denominator constant (the N-in-N*X format). Both types of frequency ratios are used to display treatment information in current clinical practises within the UK (see appendix 11). Only the N-in-N*X format was employed in the current experiment. For this reason, the next empirical question is the extent to which different frequency formats are able to influence understanding, which will be directly tested in the subsequent experiment (see chapter 5). Another limitation of the current experiment is that it was not possible to conclude which specific verbal, numerical and graphical formats could improve understanding of patients with poor skills in numerical reasoning, literacy and IQ, and those with cognitive impairments. Additional research with MS patients should be conducted to determine the efficacy of each individual format with patient groups that have these specific characteristics.

4.4.1 Conclusion

In summary, the current experiment was the first comprehensive evaluation of verbal, numerical and graphical formats on MS patients' understanding of treatment risks and benefits. The results established that different presentation methods could affect how MS patients were able to understand treatment information. However, improving

understanding did not reliably reduce patients' conflict in their treatment decisions. All findings were integrated into an updated theoretical framework of MS patients' understanding (see figure 4.3).

Based on the findings from the current experiment, it is possible to make some recommendations about the methods to improve MS patients' understanding of treatment information. Treatment risks and benefits should be presented to patients numerically where possible and verbal terms should be avoided. Specifically, frequencies are the most ideal numerical choice. In addition, numbers should be added to graphical formats to facilitate understanding. With regards to the best graphical formats, treatment information should be provided to patients using horizontal bar charts or line graphs. If pictographs are used, human or abstract figures should be arranged consecutively. Pie charts should be avoided to present treatment information. Moreover, patients with low skills in numerical reasoning, health literacy, IQ or those presenting with cognitive impairments associated with MS should be provided with additional support to ensure all patients are able to accurately understand the risks and benefits of treatments.

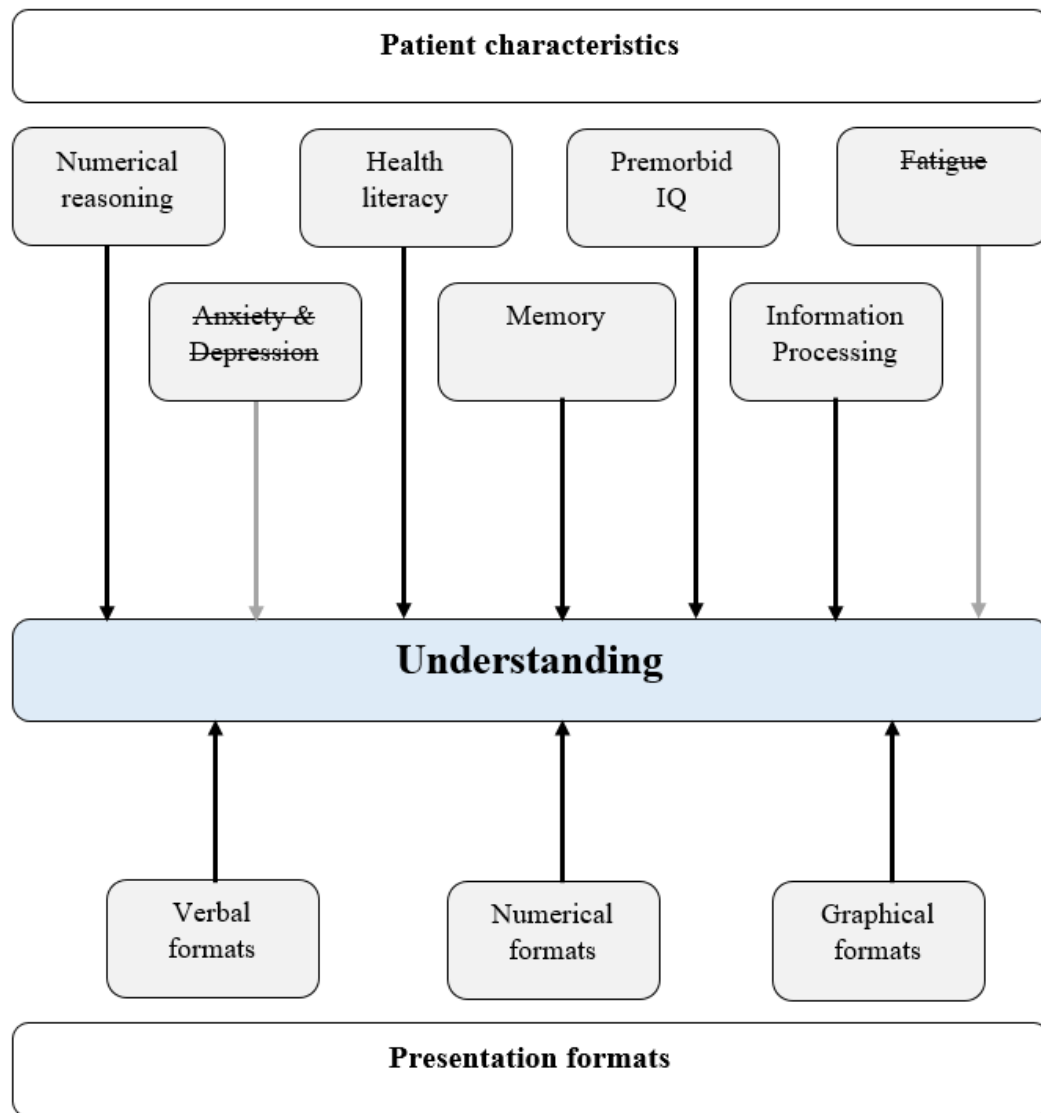


Figure 4.3 Theoretical framework 2: Factors affecting MS patients' understanding of treatment risks and benefits

Key: Black arrows, significant effects; Grey arrows, no relationship; Question, Untested factors; arrows do not signify causation

Chapter 5: Frequency ratios and framing to present treatment information

5.1 Introduction

The risk and benefit profiles of a DMD can be determined by the results of a clinical trial, whereby one group of MS patients receives the DMD of interest and are then compared with a group of patients that either take the placebo or an established DMD (Braune et al., 2015; Chahin, Balcer, Miller, Zhang, & Galetta, 2015; Fogarty et al., 2016; Maruszczak, Montgomery, Griffiths, Bergvall, & Adlard, 2015; McFarland, 2009; Miller et al., 2014). Findings from Experiment 1 showed that when MS patients were provided with information about the risks and benefits of a treatment based only on the hypothetical group of patients taking the drug, information presented in specific numerical and graphical formats could maximise MS patients' understanding (see chapter 4). For instance, frequencies were found to be an optimal method of presenting numerical information to improve MS patients' understanding of treatment risks and benefits. Yet, frequencies can also be presented using discrete ratios (e.g., either 1 in 20 or the equivalent 50 in 1000), which were not evaluated in Experiment 1. In fact, both frequency ratios are presented to patients in current clinical practise (see appendix 11). In addition, the statements that are used to present treatment information to patients can also be framed in either a positive or negative way. Framing of risks and benefits was also not manipulated in Experiment 1. Both ratios and framing to present treatment information is therefore investigated in the current experiment. These factors are also included in the theoretical framework, which is designed to indicate how MS patients' understanding of treatment information is likely to be affected (see figure 5.1).

5.1.1 Frequency ratios

5.1.1.1 Definition of frequency ratios

Numerical frequencies are an ideal way of presenting DMD information to MS patients (see chapter 4). However, frequencies can be represented using different ratios. The frequency ratio used to present risks and benefits to MS patients in Experiment 1 was the N-in-N*X format (see chapter 4). This format can be obtained by keeping the denominator constant and changing the numerator to reflect the magnitude of risks and benefits. For instance, the adverse risks of a hypothetical medication A could occur in 5 people out 1000, which may be compared to the adverse risks of a hypothetical medication B which could occur in 32 people out of 1000. Another ratio to represent frequencies can be obtained by keeping the numerator of the frequency constant at 1 and simply changing the denominator to reflect differences in magnitude of risks and benefits. This ratio is termed as the 1-in-X format. The 1-in-X ratio can be calculated by dividing the denominator by the numerator from frequencies presented in N-in-N*X format, and usually rounding up this result. Using the examples presented above, the adverse effects of medication A would occur in 1 in 200 people, whereas the adverse effects of medication B would occur in 1 in 31 people taking the drug in question.

Although frequencies are the most optimal method of providing treatment risk and benefit information to MS patients, the effect of the different frequencies on MS patients' understanding is unclear. The subsequent sections will first attempt to review evidence that has been obtained from non-clinical and non-MS populations, prior to empirically evaluating the best ratio to improve understanding in MS patients.

5.1.1.2 Review of frequency ratios in non-clinical populations

Studies with non-clinical populations reveal mixed findings with respect to different frequency ratios on understanding and decision-making. An early study presented participants with equivalent risks for a hypothetical treatment using different

ratios. For example, treatment risks were stated as occurring in either 1 person in 12,000 people or 8.3 people in 100,000 people (Halpern, Blackman, & Salzman, 1989). Participants did not differ in their treatment decisions irrespective of the frequency ratios in which the risks were presented, implying that participants are equally able to understand both frequency ratios. Note, however, that the outcome measure employed in this study was treatment choice which cannot establish patients' objective understanding of risks. In addition, the authors proposed that the absence of any effect may be due to the small differences between the numerator of the frequencies presented (i.e. 1 versus 8.3), and suggested that treatment information may need to be presented using a greater range of frequencies to detect differences in understanding based on frequency ratios (Halpern et al., 1989).

Findings from other studies have shown that frequency ratios to present risks and benefits in a medical context can affect how people understand the information. An early study assessed understanding of participants when risks were presented using different frequency ratios (Grimes & Snively, 1999). Participants showed better understanding of risks when expressed in the N-in-N*X ratio, regardless of respondent's age, language and education (Grimes & Snively, 1999). Similar findings were observed by Cuite, Weinstein, Emmons, and Colditz (2008), who randomly assigned participants to various magnitude of risks and benefits of hypothetical treatments and assessed understanding by asking participants to perform a series of operations with the risk and benefit information, such as comparing differences, halving and adding the information. The authors found that understanding of treatment risks and benefits was greatest when information was presented in percentages and frequencies using N-in-N*X format compared to the 1-in-X frequency format (Cuite et al., 2008). Although inconsistent with findings from Experiment 1 which showed that frequencies are better understood than percentages by

MS patients (see chapter 4), these findings do suggest that frequencies can be understood differently depending on the ratios.

To further demonstrate this effect, Sirota, Juanchich, Kostopoulou and Hanak (2014) conducted 5 replications of studies using non-clinical populations. The authors designed experiments using stricter criteria than existing studies comparing N-in-N*X ratios with 1-in-X ratios, namely by providing a large number of risks and benefits of a disease with a wider range of magnitudes. Participants were assessed on the probability, severity, worry and frequency of a risk using a 7-point Likert scale. The findings from all 5 experiments showed a trend towards poor understanding when frequencies were presented using the 1-in-X ratio. Specifically, probabilities of risks and benefits were considered to be higher when information was presented using the 1-in-X ratio in comparison to when presented in N-in-N*X ratio. However, this effect was statistically significant in only two experiments (Sirota et al., 2014). To determine the size of this effect, Sirota and colleagues (2014) further combined findings from 5 experiments that had been conducted with clinical populations. The authors concluded that understanding was indeed poor when information was presented in frequencies with the 1-in-X ratio, but with a considerably lower effect size than suggested by previous studies (Sirota et al., 2014).

In summary, studies conducted with non-clinical populations generally show support for frequencies presented in the N-in-N*X ratios as opposed to the 1-in-X ratio. The following section will examine the strength of this effect in clinical populations.

5.1.1.3 Evaluation of frequency ratios in clinical populations

Studies with clinical populations, although limited, consistently show that risk and benefit information for diseases are perceived as higher when frequencies are presented in the 1-in-X ratio, with no clear effect on understanding of treatment risk and benefit information. A number of studies were conducted with pregnant women who were

presented with prenatal risk of their child developing Downs syndrome at birth (Pighin et al., 2011, 2013, 2015) or adverse effects during pregnancy (Pighin et al., 2013). Numerical frequencies of this risk were presented in either N-in-N*X or 1-in-X ratio. Patients were more likely to perceive risks as larger (Pighin et al., 2011, 2015) and as more worrying (Pighin et al., 2011), and were also less able to discriminate the magnitude of the risks (Pighin et al., 2013) when these were presented using the 1-in-X frequency ratio. However, there was no difference in patients' ability to understand risk information when presented using different frequency ratios (Pighin et al., 2015).

Overall, there are a limited number of studies that have analysed how individuals understand frequencies of risks and benefits presented using different ratios, especially with clinical populations likely to make decisions based on the information. In conjunction with studies from non-clinical populations, there is some evidence to state that treatment risk and benefit information is difficult to understand when presented using the 1-in-X ratio. For this reason, researchers have discouraged the use of 1-in-X ratios when communicating risks and benefits in healthcare settings (Pighin et al., 2015; Sirota et al., 2014; Zikmund-Fisher, 2011, 2014). Yet, these ratios are employed in current clinical practise with MS patients (see appendix 11), even in the absence of empirical evidence conducted in this population.

5.1.2 Framing

5.1.2.1 Definition of the framing effect

Although numerical treatment information may clearly present treatment information, individuals may be still be biased about the magnitude of treatment risks and benefits. For instance, the outcome chosen by an individual during decision-making could vary depending on if the options are framed in positive terms (e.g. what a person stands to gain from the options) or if the options are framed in negative terms (e.g. what a person

stands to lose from the options). This phenomena is termed as the framing effect (Tversky & Kahneman, 1981; Wilson, Purdon, & Wallston, 1988).

A common example used to demonstrate the framing effect in the literature is that of an Asian disease epidemic (Tversky & Kahneman, 1981). Participants are presented a scenario in which an unusual Asian disease is expected to kill 600 people. The participants are then told that two alternative programs have been proposed to combat this disease: if Program A is adopted, 200 people can be saved and if program B is adopted, there is one third possibility that all 600 people will be saved and two thirds probability that no one will be saved. Tversky and Kahneman (1981) presented this problem to 152 students and asked them to state their preference for one of these two programs to combat the disease. Around 72% of participants stated their preference for Program A. The authors noted that this was a risk averse choice, as the prospect of certainly saving 200 lives was considered more favourable than a riskier and uncertain prospect of Program B with an equal value (i.e. a one-in-three chance of saving 600 lives in Program B is statistically equivalent to saving 200 lives in Program A). Subsequently, a new group of students were given the same problem but with two different programs. Participants were given either a choice of Program C, which if adopted would mean that 400 people will die and Program D, which offered a one third probability that nobody will die and two thirds probability that 600 people will die. Tversky and Kahneman (1981) found that 78% of 155 participants chose to take the riskier option of Program D, since the certain death of 400 people was considered less acceptable than two-in-three chance that 600 people will die, despite these options offering the same statistical outcome (i.e. a two-in-three chance that 600 people will die in program D is statistically equivalent to 400 people dying in program C). Given that the options provided for both scenarios were effectively the same, the decision to choose an option was dependent on how the information was framed. Thus, the authors concluded that people are more likely to be risk averse when

information is framed positively and more likely to be risk seeking when information is framed negatively (Tversky & Kahneman, 1981).

This effect of framing has been shown to have its roots in the influential prospect theory, first proposed by Kahneman and Tversky (1979). One key aspect of the theory is that when comparing choices during decision-making, people are likely to be influenced by the gains and losses of the choice. This is evident in the Asian disease example above, where preference for the programs were reversed when framing of the programs changed from gains to losses. According to prospect theory, the values people place on gains and losses also vary. People are likely to consider losses as more extreme than gains, which can subsequently influence the decisions they make (Kahneman & Tversky, 1979). Hence, when comparing choices during decision-making, the difference between options would be perceived as much greater if framed as a disadvantage or a loss compared to options that are framed as an advantage. Thus, people will be likely to adopt riskier programs, such as treatments, when framed in negative terms than positive terms.

In general, the framing effect explains how individuals may be biased towards an option based on the manner in which the options are framed, irrespective of the absolute risk and benefit content. Given that patients making treatment decisions are often faced with alternative treatment choices, it would be of interest to examine the effects of framing treatment information on understanding of this information. Studies have predominately looked at the effects of framing in medical contexts with non-clinical populations and with clinical populations other than MS. These studies will first be reviewed prior to evaluating the effects of framing on MS patients' understanding.

5.1.2.2 Review of framing treatment information in non-clinical populations

One of the earlier studies that explored the effects of framing in a medical context was conducted by McNeil, Pauker, Sox and Tversky (1982). Lung cancer was selected as a premise for decisions for which two alternative treatment options were presented:

radiation therapy and surgery. In reality, surgery was shown to have more patients surviving after 5 years and have a longer life expectancy in comparison to radiation therapy, indicating a better treatment choice. Participants were separated into two groups: information about therapies framed in terms of mortality or framed in terms of survival. The findings showed that 43% of participants chose radiation therapy over surgery when both therapies were framed in terms of mortality. When therapies were framed in terms of survival however, only 17% of the students chose radiation therapy. Considering that surgery was the most rational choice, it is interesting that simply framing the information positively was able to encourage people to choose the better treatment. Similar trends were observed for physicians who participated in the study (McNeil et al., 1982). The authors noted that despite physicians' considerable experience with medical data, physicians were also susceptible to the effects of framing (McNeil et al., 1982). This was further supported by another study which found that physicians made a risk-averse treatment choice when treatment information was framed in survival terms and a risk-seeking treatment choice when framed in terms of mortality (Tversky, 1986).

In further support of the framing effect as explained by the prospect theory, Meyerowitz and Chaiken (1987) assessed the impact of pamphlets framed in loss versus gains on performance of breast self-examination in non-clinical populations. Participants were randomly assigned to either of the following four conditions: pamphlets framed using gain terms (i.e. increased survival if performing breast self-examination), pamphlets framed using loss terms (i.e. decreased survival of not performing breast self-examination), pamphlets with neutral language or no pamphlets about breast self-examination. At a 4-month follow up, participants who received the pamphlet in the loss frame reported engaging in breast self-examination significantly more often than participants in the other three conditions. Likewise, participants in another study were assessed for their risk perception following equivalent medication information framed in

either a positive, negative or a combination of both frames (Peters et al., 2011). Participants provided with information in positive frame perceived the medication to be less risky in comparison to people given information framed negatively or in a combination frame. These studies further provide support for a framing effect in the context of treatment decision-making based on the prospect theory.

Conversely, some studies with non-clinical population groups have shown effects of framing on an individual's decision but in the opposite direction to that explained by the prospect theory. Wilson, Kaplan and Schneiderman (1987) presented non-clinical population groups with a hypothetical medical scenario and a choice of two alternative treatments. A framing effect was observed. Only 28% of the subjects reported they would seek surgery for the hypothetical condition if the surgery was framed in terms of 90 per cent dying, whereas 46% of students chose to take the surgery if framed as 10 per cent surviving the surgery (Wilson et al., 1987). That is, people were willing to take treatments if framed in terms of surviving rather than in terms of dying, contrary to the prospect theory. Even though the risk and benefit information for both treatments were statistically equivalent, it may be assumed that understanding of treatment information was influenced by the framing of the information which subsequently affected the decision for the treatment. However, objective understanding was not measured in this study. Similar findings were observed in the study by Marteau (1989). One of their experiment focused on presenting the outcomes associated with surgery in a positive frame or a negative frame. Probabilities for the outcomes of surgery were manipulated to either: 10 per cent chance of dying/90 per cent chance of surviving, 40 per cent chance of dying/60 per cent chance of surviving or 60 per cent chance of dying/40 per cent chance of surviving. Marteau (1989) found that significantly more people chose to take surgery when the risk of surgery was framed as 10 per cent chance of survival compared to 90 per cent chance

of death. Overall, more people chose the option of surgery when the information was framed in terms of survival than when it was presented in terms of dying.

There are a number of explanations for these inconsistent effects of framing on decisions across studies. The inconsistencies may be due to the different types of options that could be differently framed. For instance, although the prospect theory suggests that people are more likely to choose riskier options when information is framed negatively, this may only apply when people are presented with two competing options, with one being a risky option and the other a riskless option (Tversky & Kahneman, 1981). Another explanation for the differences in decisions of participants in these could be due to the general aim of the options. For instance, a review by Rothman, Bartels, Wlaschin and Salovey (2006) found that loss-framed messages were more effective when options that were provided to patients were about detecting the presence of a disease. To note, an updated review found very minimal effects of loss-based framed messages on detecting the presence of disease (O’Keefe & Jensen, 2009). In contrast, when the options that were framed were about prevention of a disease, such as by taking a medication, gain-framed messages were more likely to be influential (Gallagher & Updegraff, 2012; Rothman et al., 2006). Although findings against and in support of the prospect theory show that framing of information can impact decisions for equivalent options, it was not possible to determine whether changes in decisions for options were due to differences in comprehension of information when framed in different ways.

Only two studies have assessed understanding when information is framed differently. Armstrong, Schwartz, Fitzgerald, Putt and Ubel, (2002) assessed both understanding and preferences for a hypothetical treatment in non-clinical populations. Participants were presented with graphs and numerical information framed in either the chance of surviving after taking the treatment, the chance of mortality after taking the treatment, or a combination frame stating both the chance of survival and mortality, prior

to assessing participants' understanding of the information. Participants who received the benefits of treatments in terms of surviving or in a combination of both frames, showed significantly greater understanding compared to treatment information provided in a negative frame (Armstrong et al., 2002). As expected from previous studies, the preference towards a treatment also varied by framing. However, inconsistent with the prospect theory, preventative treatment were more likely to be adopted when framed in a positive manner (Armstrong et al., 2002). In another study, non-clinical populations were presented treatment information in either positive or negative frames and patients' decision to take the treatment was recorded (Carling et al., 2010). All participants were then given more detailed information about the treatment, which the authors presumed will lead to informed treatment decisions. Findings showed that participants provided with treatment information in a positive frame were more likely to choose treatments consistent with treatments chosen following information provided comprehensively. From this, the authors were able to conclude that understanding was greater for information presented in a positive frame (Carling et al., 2010).

In sum, studies with non-clinical populations show that framing of information can influence decisions made about numerically equivalent options. However, the decision to choose an option based on a particular type of frame was inconsistent between studies. Only two studies have specifically assessed understanding of information when framed differently in non-clinical populations. Positively framed information was more likely to increase understanding of treatment information in comparison to negatively framed information. The following section will explore whether the effects of framing are also evident in clinical populations, given that clinical populations are directly affected by medical information.

5.1.2.3 Review of framing treatment information in clinical populations

One study found an effect of framing on decisions to take hypothetical treatments in clinical populations. Consistent with findings observed in non-clinical populations, the study conducted by McNeil and others (1982) found that patients showed an effect of framing, as the option of riskier surgery was chosen when information was framed in terms of living compared to mortality.

However, the framing effect for participating in a clinical trial was not observed for cancer patients in another study (Llewellyn-Thomas, McGreal, & Thiel, 1995). Rather, the decision to take part in a clinical trial was mostly effected by age, sex and education of patients. The authors concluded that patient characteristics may be a more sensitive predictor for decisions based in real clinical contexts, instead of how information is framed. Similarly, when breast cancer patients were given information about risks and benefits of treatment, the framing of treatment risks and benefits did not influence the choice to take the treatment (Zimmermann, Baldo, & Molino, 2000). Instead, the choice of taking a treatment was dependent on the risk and benefit profiles of treatments. These findings were further supported by a review of the literature of clinical populations conducted by Edwards, Elwyn, Covey, Matthews and Pill (2001). Overall, the review did not discover any statistically significant effect of framing treatment information positively or negatively, with inconsistent trends for positive and negative framing of information on the decision to choose a treatment. However, these studies do not necessarily rule out the possibility that patients' understanding of treatment information could be affected by how treatment information is framed.

More recently, a study looked at patients' preferences for different ways of expressing treatment risk and benefits, including how information was framed (Raval, Goodyear-Smith, & Wells, 2015). Patients in the study showed a consistent preference for treatment risks when framed positively. The authors suggested that these preferences

could be based on information which was easier to understand (Raval et al., 2015). However, it is not possible to draw such conclusions without objectively assessing understanding of treatment risks and benefits in patients.

Overall, framing has been shown to affect decisions in non-clinical populations and physicians, but with limited evidence in clinical populations. Only two studies assessed understanding of non-clinical populations when information was framed differently and found that people better understood information framed positively. No studies have looked at the effects of framing on MS patients' understanding.

5.1.3 Patient understanding and decisional conflict

Patients' understanding of treatment risks and benefits could have an impact on how conflicted patients feel about their treatment choice (Janis & Mann, 1977; O'Connor, 1995) (see section 4.1.5). Some studies have shown that treatment decisions can alternate depending on the ratios used to present frequencies (Halpern et al., 1989). In terms of framing, several studies have shown that decisions between equivalent outcomes can depend on how information is framed (Kühberger, 1998; Peng, Jiang, Miao, Li, & Xiao, 2013; Perneger & Agoritsas, 2011; Tversky, 1986; Zipkin et al., 2014). It is therefore reasonable to assume that patients' conflict in treatment decisions can depend on the frequency ratios and the manner in which treatment information is framed. However, this relationship has not been previously explored in the context of treatment decisions.

5.1.4 Patient understanding and patient characteristics

The ability to accurately understand treatment information may also be moderated by factors other than frequency ratios and framing of the informational content.

5.1.4.1 Numerical reasoning, health literacy and IQ

Numeracy skills were shown to moderate comprehension of information provided in different frequency ratios within one study (Reyna & Nelson, 2010), but not in others

(Oudhoff & Timmermans, 2015; Sirota et al., 2014). People with poor numeracy skills were also found to be more susceptible to the effects of framing across studies (Garcia-Retamero & Galesic, 2010a; Peters & Levin, 2008; Reyna & Nelson, 2010). Although these findings are inconsistent, it is likely that numerical reasoning will play a role in MS patients' understanding of information depending on framing and frequency ratios.

No studies have explored the relationship between health literacy and IQ on understanding of treatment information when presented in different frequency ratios frames or different frames.

5.1.4.2 Symptoms of MS

MS patients with cognitive and affective symptoms may be particularly susceptible to poor understanding when information is presented in different frequency ratios or frames. These symptoms include: fatigue, depression, anxiety, deficits in information processing-speed and impairments in working memory (see section 1.1.2 for overview on MS patient symptoms).

5.1.5 Research questions and hypothesis

The following study addressed three specific questions based on the findings from the review, as represented in the theoretical framework below (see figure 5.1). First, which ratios should be used to present frequencies of treatment risks and benefits (N-in-N*X ratio/1-in-X ratio) to maximise MS patients' understanding? Second, how should treatment risk and benefit information be framed (positive frame/negative frame/combined frame) to maximise MS patients' understanding? Finally, what is the relationship between MS patients' understanding of treatment information presented in different frequency ratios and frames, and patients' conflict in their treatment decisions? Additional exploratory questions attempted to address how numerical reasoning, health literacy, premorbid IQ and symptoms of MS could impact MS patients' understanding of information presented in different frames and frequency ratios?

Specific hypotheses for the current experiment was derived from studies with non-clinical and clinical populations and were as follows:

- (i) N-in-N*X ratio would maximise understanding compared to the 1-in-X format;
- (ii) Positively framed treatment risk and benefit information will maximise understanding compared to negative frames and combination frames;
- (iii) Greater understanding of treatment information will reduce decisional conflict in MS patients;
- (iv) Numerical reasoning will be positively related to understanding of information.

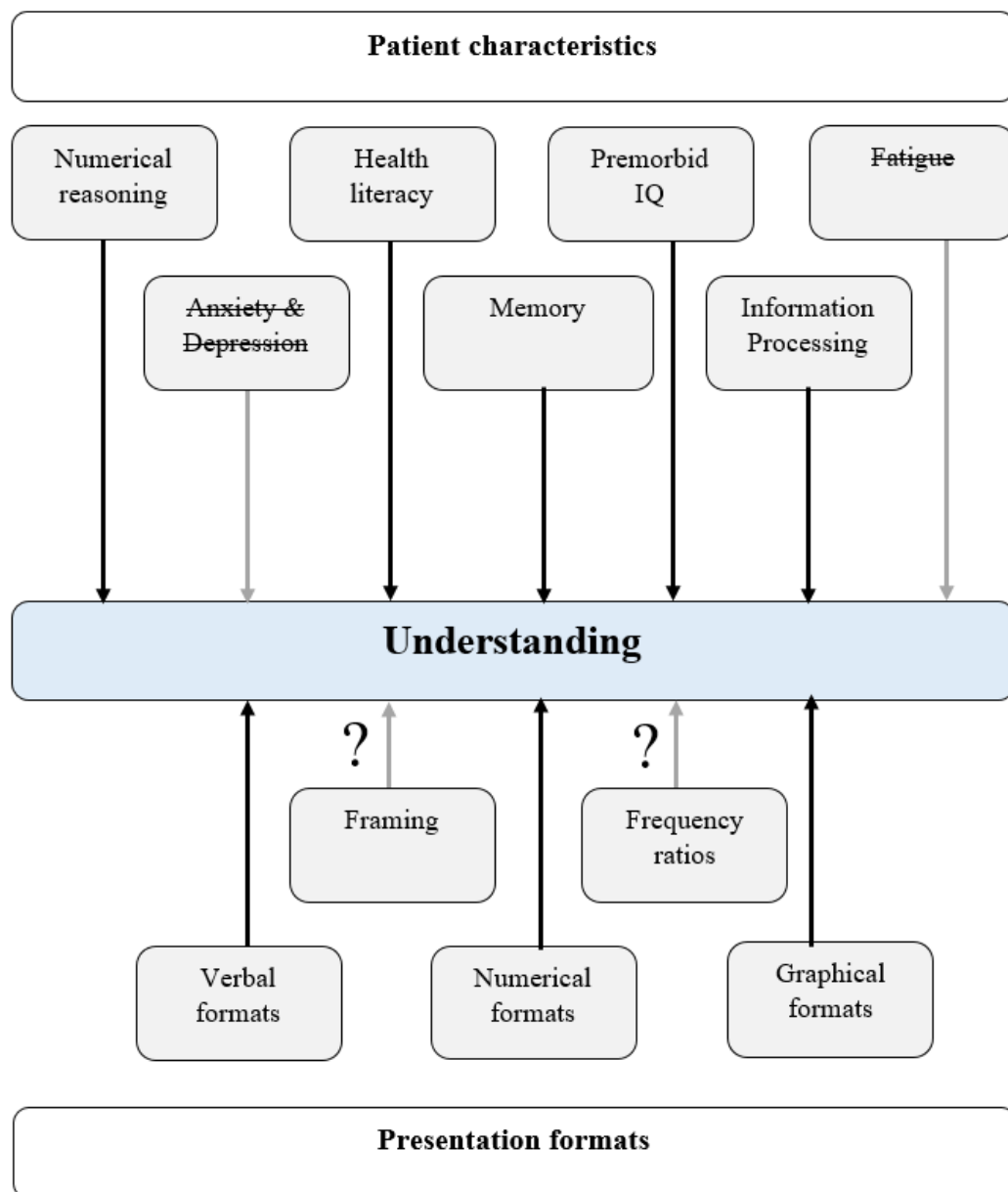


Figure 5.1 Theoretical framework 3: Factors affecting MS patients' understanding of treatment risks and benefits

Key: Black arrows, significant effect; Grey arrows, no relationship; Question, Untested factors; arrows do not signify causation

5.2 Experiment 2 methodology

5.2.1 Participants

A total of 45 relapsing-remitting MS patients took part in this study, which includes 33 patients that had previously taken part in experiment 1. The inclusion and criteria for eligibility to take part was the same as in experiment 1 (see section 4.2.1).

5.2.2 Materials and design

The current study employed a cross-sectional within-subject design in order to assess patients' understanding of treatment risks and benefits, and their conflict for their treatment decisions when treatments were presented in different frequency ratios and frames.

One hypothetical disease was included in this study, for which risk and benefit information was provided for two hypothetical treatments. The name and symptoms of the disease were new in the current experiment, but mimicked the progressive nature of MS similar to Experiment 1 (see appendix 15 for hypothetical disease). Treatment names, and the associated risks and benefits of the treatments were also new in the current study, but were checked by a small survey sample as discussed in Experiment 1 (see section 4.2.2). However, the risk-benefit profiles of the treatments were deliberately manipulated to mimic risk-benefit profiles of first-line and second-line DMDs (i.e. one treatment offered high risks and high benefits, and one treatment offered low risks and low benefits).

Each hypothetical treatment presented information for a minor risk, an adverse risk and two possible benefits of taking the treatment based on a clinical trial conducted with patients for 1 year, 2 years and 5 years. Participants were informed that the information they would see denotes a hypothetical clinical trial where the intervention group refers to the group of patients taking the treatment and the control group refers to a group of patients with the same disease taking a placebo drug which does not have any

effect on the disease (i.e. this group essentially did not take a treatment). Patients were further informed that presenting information about two groups in a clinical trial will help them to see treatment risks and benefits in the context of clinical trial data.

Patients were presented with information framed in three different ways for both treatment risks (minor and adverse) and treatment benefits. Thus, there were a total of six treatment outcomes presented in three frames (positive, negative and combined frame). Patients were also presented with frequencies in either N-in-N*X ratio or 1-in-X ratio. Hence, in total, patients were presented with 8 different formats across two treatments (see appendix 16 for presentation formats presented in treatment 1).

The order of all six framing conditions were randomised between either a treatment risk (minor and adverse) or benefit. The order of the ratios was subsequently randomised to the remaining treatment risk and benefit (see table 5.1). To further reduce any effects of order, the treatments were counterbalanced between patients.

Table 5.1 Order of framing and frequency ratios presented in Experiment 2

Treatment	Outcome	Method of communicating differences
Treatment 1	Adverse risk	Combined frame
Treatment 1	Minor risk	Positive frame
Treatment 1	Benefit	Positive frame
Treatment 1	Benefit	1-in-X
Treatment 2	Adverse risk	Negative frame
Treatment 2	Minor risk	N-in-N*X frame
Treatment 2	Benefit	Combined frame
Treatment 2	Benefit	Negative frame

Treatment 1 was named Sprantil; Treatment 2 was named Mylobryne

The main outcome measures employed in the current experiment were patient understanding and conflict in treatment decisions.

The patient understanding measure was similar to that used in Experiment 1 but with the addition of new questions to reflect information provided for both intervention and control group of a hypothetical clinical trial. Similar to Experiment 1, the first question directly assessed the magnitude of minor risks, adverse risks and benefits of the treatments based on the intervention group of a clinical trial. This was a free-recall question. The second question was added for the purpose of the current experiment. This question required patients to calculate differences in treatment risks and benefits from patients in the intervention group and patients in the control group of a hypothetical clinical trial (see appendix 16 for example of questions presented to patients). Calculating differences as a method of assessing understanding the treatment information has also been used by Cuite and colleagues (2008). Given that poor numeracy skills may affect the ability to calculate differences between groups, a multiple choice format was provided for this question. Patients were provided a total of 4 possible answers and were told that all multiple choice values were an approximate number only. Patients were asked to choose one answer that was the closest to the true difference and were awarded 1 point for answers that were correct. No score was awarded if patients chose an incorrect answer or did not answer the question. The filler answers in the multiple choice were randomly modified throughout the questions to avoid patients guessing at the correct answer based on repetition of filler answers. With the addition of this question to the patient understanding question, patients were able to get two points for every treatment minor risk, adverse risk and benefit that was provided. Given that each treatment outcome was presented for 1, 2 and 5 years of taking the clinical trial, the maximum score for each treatment risk (minor and adverse) and benefit was 6 points. The maximum understanding score for each treatment was 24 points, based on information provided for one minor risk,

one adverse risk and two possible benefits of taking the treatment (i.e. 4 possible outcomes for one treatment). The total understanding score across both treatments was therefore 48 points.

The decisional conflict measure was the same as that employed in experiment 1 (see section 4.2.2.2).

All other assessments presented to patients throughout the study were also the same as those provided in Experiment 1, and includes: patient demographics, numerical reasoning, health literacy, premorbid IQ, and cognitive and affective symptoms of MS.

5.2.3 Procedure

The procedure for recruiting interested patients from the two hospital clinics was the same as discussed in Experiment 1 (see section 4.2.3). Following consent, an appointment was made with patients to take part in the study. The study was conducted either at the clinics or at the patient's home, depending on patients' preference. The study took approximately 2 hours to complete and was conducted face-to-face using offline materials only.

Initially, patients were presented with the visual acuity scale to ensure they were eligible to view the remaining study (see section 4.2.1). If eligible to continue, patients were asked demographic questions and assessed on the disability status scale. Next, patient characteristics were measured in the following order: health literacy, numerical reasoning, depression and anxiety, fatigue and premorbid IQ. All patients were then shown information about one hypothetical chronic medical disease followed by two hypothetical treatments. Comprehension questions to assess understanding were provided after each treatment outcome. Patients were also required to make their treatment choice and complete the DCS measure after viewing both treatments. Finally, the BICAMS measure was conducted with patients at the end of the study. Note, however, that since this experiment was conducted alongside Experiment 3, all measures (aside from the

main task) were only measured once. Both Experiment 3 and the current experiment were conducted in alternating order between patients.

5.2.4 Sample size

Sample size was calculated to detect an effect on MS patients' understanding of treatment risks and benefits. The calculation was similar to that given in Experiment 1 (see section 4.2.4) and required a minimum sample of 45 MS patients.

5.2.5 Statistical analysis

All statistical analyses were carried out using SPSS 21. Means and standard deviations were provided for all continuous data. Maximum scores were given for all assessments in the study. A test of normality was conducted for the understanding outcome measure for each format using the Shapiro-Wilks test. The assumption of normality was significantly violated for all ratios and framing ($p < .001$) and therefore a nonparametric Friedman analysis of variance was conducted. Where the Friedman test was significant, pairwise comparisons were conducted by using the nonparametric Wilcoxon Signed Ranks test. Bonferroni corrections were applied for multiple comparisons. Effect sizes are calculated for all pairwise comparisons by dividing the z score by the square root of total number of observations, based on Rosenthal's formula (Rosenthal, 1994); where, 0.1, 0.3 and 0.5 equates to small, medium and large effect sizes, respectively. For the purpose of the analysis, several formats were sometimes collapsed into one average understanding score.

A bivariate Pearson's product moment correlation was conducted to assess the relationship between patient understanding and the standardised scores of the DCS, including all subscales. Bivariate Pearson's product-moment correlations were also computed to assess the relationship between understanding and raw scores on measures of numerical reasoning, health literacy, premorbid IQ and symptoms of MS. Due to multiple correlations, a stringent alpha of $p < .01$ was applied and accepted as significant.

5.3 Results

5.3.1 Patient demographics

A total of 45 patients took part in this experiment. Demographic information for patients are displayed in Table 5.2.

5.3.2 The effect of frequency ratios on patients' understanding

There was a statistically significant difference in understanding scores for frequency ratios (1-in-X ratio, N-in-N*X ratio), $X^2(1) = 44.000$, $p < .001$. According to mean scores, understanding was greater for N-in-N*X ratio ($M=5.67$, $SD=.64$) compared to 1-in-X ratio ($M=.67$, $SD=1.15$, $z=-5.869$, $r=0.61$)

5.3.3 The effect of framing on patients' understanding

There was a statistically significant difference in framing across risks and benefits of treatments (positive framing, negative framing, combined framing) on patients' understanding, $X^2(2) = 10.227$, $p < .01$. Pairwise comparisons were conducted to statistically compare the means for positive frames ($M=4.83$, $SD=1.37$), negative frames ($M=5.25$, $SD=.90$) and combined frames ($M=4.81$, $SD=1.18$). Understanding was greater for negative framing compared to positive frames ($z=-2.995$, $r=0.31$, $p < .01$) and combined frames ($z=-2.519$, $r=0.27$, $p < .05$). There was no significant difference between positive frames and combined frames ($z=-.301$, $p=.763$).

There was no statistically significant difference when framing was manipulated for risks and when framing was manipulated for benefits, $X^2(1) = .243$, $p=.622$.

Table 5.2 Patient demographics and disease status for Experiment 2 (n=45)

	Mean (SD)	n (%)
Age, years	46.76 (10.50)	
Gender		
Female		36 (80.0)
Male		9 (20.0)
Level of education		
High school		15 (33.3)
College		11 (24.4)
Bachelor's degree		8 (17.8)
Postgraduate		11 (24.4)
Employment status		
Full-time (>16 hours)		13 (28.9)
Part-time (<16 hours)		10 (22.2)
Self-employed		7 (15.6)
Unemployed		11 (24.4)
Medical leave		3 (6.7)
Retired		1 (2.2)
Time since MS diagnosis, years	10.89 (8.51)	
HAI disability scale	1.64 (1.77)	
Current DMD		
Interferon betas		15 (33.3)
Glatiramer Acetate		4 (8.9)
Teriflunomide		0 (0)
Fingolimod		8 (17.8)
Alemtuzumab		4 (8.9)
Dimethyl Fumarate		5 (11.1)
Natalizumab		8 (17.8)
Mitoxantrone		1 (2.2)

DMD= disease-modifying drugs; HAI = Hauser Ambulation Index

* Score of 1 on HAI scale = Able to walk normally but report fatigue interfering with athletic activities

5.3.4 Patient understanding and decisional conflict

A bivariate Pearson product-moment correlation showed no significant correlation between patients' understanding and the total decisional conflict score. There were also no significant correlations between understanding of treatment information and any other DCS subscales (see table 5.3).

Table 5.3 Correlations between patient understanding and decisional conflict

	Max scores	Mean	SD	Correlation
Total understanding	48	36.13	6.24	
DCS informed	100	15.37	14.43	-.265
DCS values	100	25.00	20.26	-.127
DCS support	100	23.15	16.94	-.159
DCS uncertainty	100	42.77	23.21	-.125
DCS effective	100	43.89	30.07	-.218
DCS total score	100	28.13	17.30	-.207

* = indicates significance at $p < .05$ level; ** at $p < .01$ level; *** at $p < .001$ level; DCS, Decisional conflict scale

5.3.5 Patient understanding and patient characteristics

Patients were assessed for numerical reasoning skills, health literacy, premorbid IQ and MS symptoms in the current experiment. As shown in table 5.4, MS patients in this experiment mostly showed symptoms of fatigue and cognitive impairments. A bivariate Pearson product-moment correlation coefficient was computed to assess the relationship between treatment understanding score and symptoms of MS. Means, standard deviations and correlations for all assessments are presented below (see table 5.5). There were significant correlations between understanding of treatment information with numerical reasoning ($r = .509$, $p < .001$), premorbid IQ ($r = .393$, $p < .01$), information processing speed ($r = .462$, $p < .01$), verbal memory ($r = .462$, $p < .01$) and visual memory ($r = .382$, $p = .01$).

There was no significant relationship between understanding of treatment information with health literacy, anxiety, depression, fatigue and visual memory.

Table 5.4 Patients impaired on assessments of numerical reasoning, health literacy, premorbid IQ and MS symptoms (n=45)

Patient characteristics and MS symptoms	n (%)
Health literacy	6 (13.3)
Numerical reasoning	3 (6.7)
Depression	1 (2.2)
Anxiety	5 (11.1)
Fatigue	22 (48.9)
Premorbid IQ	3 (6.7)
Information processing speed	14 (31.1)
Verbal memory	15 (33.3)
Visual memory	23 (51.1)

Table 5.5 Correlations between patient understanding and patient characteristics

Patient characteristics	Max scores	Mean	SD	Correlation
Total understanding	48	36.13	6.24	-
Numerical reasoning	25	16.36	3.80	.509***
Health literacy	8	7.42	1.32	.175
Anxiety	21	6.27	3.98	-.118
Depression	21	4.11	3.69	-.059
Fatigue	63	44.00	13.47	-.087
Premorbid IQ	50	36.69	8.46	.393**
Information processing speed	110	56.62	12.62	.462**
Verbal memory	80	49.07	12.43	.466**
Visual memory	36	21.16	6.46	.382**

* = indicates significance at p<.05 level; ** at p<.01 level; *** at p<.001 level, correlations in bold accepted as significant due to multiple correlations.

5.4 Discussion

Studies with both non-clinical and clinical populations have generally shown that frequencies presented in the 1-in-X ratio are more difficult to understand. The current experiment was the first to evaluate MS patients' understanding of treatment risks and benefits when presented using frequencies with different ratios. Consistent with findings from a range of population groups, MS patients also showed poor understanding of frequencies presented in the 1-in-X ratios in comparison to N-in-N*X ratios. Considering that frequencies in the N-in-N*X ratio are also better than percentages at improving MS patients' understanding as demonstrated by Experiment 1 (see chapter 4), further indicates that N-in-N*X ratios are the best way to present quantitative treatment risk and benefit information to MS patients.

Several explanations have been proposed for the difficulty in comprehending frequencies presented in the 1-in-X format. Given that the 1-in-X ratio has shown to lead to overestimation of treatment risks and benefits in clinical populations, it has been suggested that this effect may be due to underestimation of frequencies presented in N-in-N*X ratios (Pighin et al., 2011, 2015). Unlike these studies, the current experiment employed a within-subject design and it was therefore not possible to assess the under and overestimation of equivalent risks and benefits across patients. However, the current study was able to show that objective understanding was greater for frequencies in the N-in-N*X format, indicating that underestimation of N-in-N*X ratios were not the reason for overestimation of frequencies based on the 1-in-X ratio.

Another explanation is that the 1-in-X effect has similar underpinnings to other well-known ratio effects, including: numerator neglect, denominator neglect and group-diffusion. Numerator neglect refers to individuals focusing only on different denominators between ratios (Yamagishi, 1997), as these are typically smaller in the case of 1-in-X compared to N-in-N*X. However, Pighin and colleagues (2011) found no

differences in patients' understanding when the denominators were increased from 48 to 160. Denominator neglect, on the other hand, refers to people simply focusing on the numerator of the ratios and neglecting the denominator (Miller, Turnbull, & McFarland, 1989). Considering that the 1-in-X ratio always has a numerator of 1, the denominator neglect theory would predict that the 1-in-X frequencies would be perceived as lower than N-in-N*X. However, the opposite effect is evident for frequencies presented using the 1-in-X ratio (Pighin et al., 2011, 2015; Sirota et al., 2014). The group-diffusion effect is another commonly known ratio effect which suggests that the larger the denominator, the lower the perceived probability of developing a risk due to the illusion of being a member of a larger group (i.e. 5 in 60 should be perceived as lower than 1 in 12) (Yamagishi, 1997). However, this effect has not been replicated in frequencies presented with both the numerator and denominator present, such as the 1-in-X ratio (Price et al., 2007; Sirota et al., 2014). In sum, although the 1-in-X cannot be easily comprehended, the theoretical reason for this effect is not clearly understood. Regardless, recommendations may be made for the use of N-in-N*X ratios when presenting treatment risk and benefit information.

The current experiment also aimed to determine how framing of treatment information could affect MS patients' understanding. The results showed that treatment risks and benefits framed negatively (e.g. the number of people who will have a treatment risk, and the number of people who will not show a delay in the disease symptoms, respectively) was easier to understand by MS patients than treatment risks and benefits framed positively or in a combination of both frames. This is contrary to a previous study which found that hypothetical treatment information framed positively was easier to understand, compared to negative or combined frames (Armstrong et al., 2002). The differences between this study and the current experiment may be due to two reasons. Firstly, both studies differed in respect to the treatment information that was manipulated

using different frames. Whilst Armstrong and colleagues (2002) used survival and mortality curves for treatments framed positively and negatively, respectively, the current experiment framed a wide range of treatment risks and benefits differently. Secondly, the study by Armstrong and colleagues (2002) employed non-clinical populations, whereas the current experiment assessed MS patients who are more likely to make decisions based on the information framed in different ways. In fact, disparities between non-clinical and clinical populations are also evident when looking at the effects of framing on decision-making, as studies with non-clinical populations generally observe a framing effect (Abhyankar, Summers, Velikova, & Bekker, 2014; Armstrong et al., 2002; Carling et al., 2010; Gallagher & Updegraff, 2012; Marteau, 1989; Meyerowitz & Chaiken, 1987; Peters et al., 2011; Wilson et al., 1987), whereas studies with clinical populations have not shown a consistent effect on decisions based on framing (Llewellyn-Thomas et al., 1995; McNeil et al., 1982; Zimmermann et al., 2000). This indicates that the context in which information is provided may play an important role in the extent to which framing can affect decisions or understanding in individuals.

Strategies have been proposed to reduce any effects of framing on understanding and decision-making. In a study conducted by Almashat, Ayotte, Edelstein and Margrett (2008), participants that listed all the risks and benefits of a treatment, regardless of the framing, were less susceptible to the effects of framing when compared to a group who did not employ this strategy. However, such a strategy would not be applicable in the context of providing DMD risks and benefits to MS patients given the time-consuming nature of the task. Another strategy was proposed by Garcia-Retamero and Galesic (2010), who found that the addition of graphical formats, particularly bar charts and pie charts, was able to eliminate the effects of framing. Consistent with this strategy, Experiment 1 has shown that particular graphical formats are able to improve understanding of patients with MS. Although, pie charts were shown to be the least

understood graphical format according to Experiment 1. In general, given the low effect size for the impact of framing on patients' understanding in the current experiment and the inconsistent effects of framing in previous studies, it is likely that framing treatment information negatively only marginally improves understanding. However, it seems that any effects of framing on patients' understanding could further be reduced by addition of graphical formats.

The current experiment also explored the relationship between treatment understanding scores with patients' characteristics, including symptoms of MS. As predicted, numerical reasoning showed a significant positive relationship with understanding of treatment risk and benefit information. This was supported by some studies for both frequency ratios and framing of information (Garcia-Retamero & Galesic, 2010a; Peters & Levin, 2008; Reyna & Nelson, 2010), but not others (Oudhoff & Timmermans, 2015; Sirota et al., 2014). Interestingly, significant relationships were also observed with impairments in verbal memory, visual memory and information processing speed indicating that MS patients with cognitive impairments may be particularly susceptible to information framed in different ways and presented using different frequency ratios. Presenting treatment information only using the N-in-N*X frequency ratios can likely improve understanding in these patients.

Although the current experiment is the first to explore the effects of framing and frequency ratios on MS patients' understanding and their conflict for treatment decisions, there are a number of limitations present. First, framing and frequency ratios were not assessed separately in this experiment, which meant that total scores of understanding and decisional conflict used in correlations were a combination of both framing and frequency ratios. However, the experiment was designed in order to use the minimal number of patients and yet still investigate the impact of framing and frequency ratios. Second, information provided throughout the experiment was for two groups of patients in a

clinical trial context. However, this experiment did not assess whether the methods to communicate differences between groups could also affect patients' understanding of treatment risks and benefits. This will be explored in a subsequent experiment.

5.4.1 Conclusion

Despite the limitations, the present experiment indicates that the ratios used to present frequencies can have an effect on MS patients' understanding of treatment risks and benefits. Understanding for treatment information could be maximised if presented using the N-in-N*X ratio. In addition, the frames used to present information could further influence treatment understanding in MS patients, with risks and benefits presented in negative frames more likely to improve understanding. However, the effects of framing on patients' understanding is likely to be very low. MS patients with low numerical reasoning skills and increased cognitive impairments may be particularly susceptible to the effects of ratios and framing of treatment information. These findings were integrated into an updated theoretical framework of MS patients' understanding (see figure 5.2).

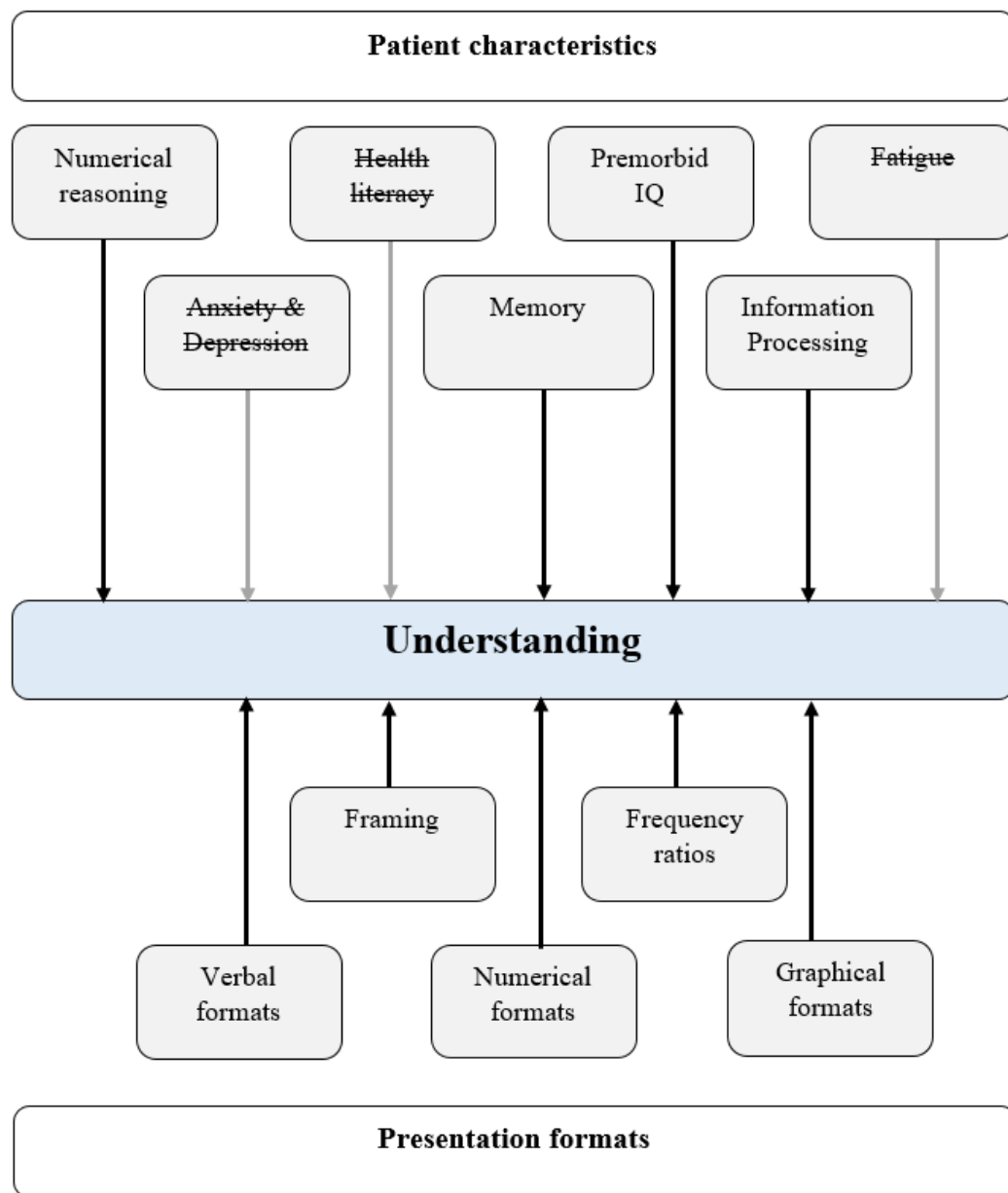


Figure 5.2 Theoretical framework 4: Factors affecting MS patients' understanding of treatment risks and benefits

Key: Black arrows, significant effect; Grey arrows, no relationship; Question, Untested factors; arrows do not signify causation

Chapter 6: Methods to communicate treatment differences from groups in clinical trials

6.1 Introduction

Experiment 2 presented patients with treatment information from a hypothetical clinical trial based on two groups: an intervention group in which patients receive the treatment of interest and a placebo group in which patients do not take a treatment. Yet, the differences between these groups were not clearly communicated to MS patients. It is possible that communicating these differences could maximise MS patients' understanding of the differences between groups of a clinical trial, and help determine the risks and benefits of a treatment. There are a number of methods which can be used to communicate such differences between two groups, and include: absolute terms, relative terms and numbers needed to treat or harm. The most effective method of communicating these differences to MS patients needs to be identified.

The effectiveness of these methods on understanding risks and benefits have been primarily assessed with non-clinical populations and clinical populations other than MS. The best method to communicate differences between clinical trial groups to MS patients is unclear. Yet, relative terms are frequently used to display treatment benefits to patients with MS in current clinical practise in the UK (see appendix 11). The current chapter will first aim to define all these methods of communicating differences between groups. Second, findings from both non-clinical and clinical populations will be reviewed to identify the best method of communicating risk and benefits differences. Finally, a study will be conducted directly with MS patients to evaluate the best method of improving understanding in MS patients.

6.1.1 Definition of methods to communicate differences between groups

Several methods can be used to communicate differences between risks and benefits of two groups, such as the groups within a clinical trial. These methods vary in the calculations to obtain these differences. To better explain these calculations, some example data from a faux clinical trial is presented in table 6.1 and the formulas used to calculate these methods are presented in table 6.2. Additionally, the following terms will be used to define the different methods of communicating differences: event rate (ER), experimental event rate (EER) and control event rate (CER): where ER refers to the risk or benefit of a treatment, EER refers to the ER of the intervention group of a clinical trial (i.e. patients taking the treatment of interest), and CER refers to ER of a control group of the clinical trial (i.e. patients taking the placebo or an existing treatment). The EER and CER may be added to the beginning of any method and this additional information is termed the baseline information.

Table 6.1 Example data to calculate differences between risks and benefits of clinical trial groups

	Risk increase (risks)		Risk reduction (benefits)	
	Experimental/ intervention group (E)	Control/ placebo group (C)	Experimental/ intervention group (E)	Control/ placebo group (C)
Events	3	1	150	50
Total subjects	1000	1000	1000	1000
Event rate (ER)	3 (0.3%)	1 (0.1%)	150 (15%)	50 (5%)

Table 6.2 Formulas to calculate differences between risks and benefits of clinical trial groups

Methods	Abbr.	Formula	Example data from table 6.1
Absolute risk increase (risk)	ARI	$EER - CER$	100 (10%)
Absolute risk reduction (benefit)	ARR	$EER - CER$	2 (0.2%)
Relative risk increase (risk)	RRI	$(EER - CER) / CER$	Double (200%)
Relative risk reduction (benefit)	RRR	$(EER - CER) / CER$	Double (200%)
Numbers needed to harm (risk)	NNH	$1 / (EER - CER)$	10
Number needed to treat (benefit)	NNT	$1 / (EER - CER)$	500

Abbr., abbreviation; CER, control group rate; EER, experimental group rate

6.1.1.1 Absolute risk increase and absolute risk reduction

Absolute risk increase (ARI) and absolute risk reduction (ARR) refers to the difference between the event rate of the intervention and control group of a clinical trial (i.e. $EER - CER$). With the example data presented in table 6.1, the absolute risk increase between the intervention and control will be 2 (i.e. $3 - 1 = 2$) and the absolute risk reduction will be 100 (i.e. $150 - 50 = 100$). The absolute risk differences can be larger or smaller depending on the size of the original event rate.

To communicate the differences between the risks of the intervention group and the risks of the control group using the ARI method, the following statement may be presented to patients: “compared to the control group, 2 more people out of 1000 people will show an increase in the risk of developing the adverse effect when taking the medication”. Similarly, to communicate the differences between the benefits of the intervention group and the benefits of the control group using the ARR method, the following statement may be used: “compared to the control group, 100 more people out of 1000 people will show a benefit of the disease symptom when taking the medication”. Absolute terms can also be conveyed in the form of percentages (Covey, 2007; Raval et

al., 2015). Thus, the risks could be stated as: “compared to a placebo group, 0.2% more people will show an increase in the risk of adverse effect when taking the medication”. Likewise, using percentages to communicate the benefits, the following statement could be used: “compared to the placebo group, 10% more patients will show a benefit in terms of the disease symptom when taking the medication”.

5.1.4 Relative risk increase and relative risk reduction

Relative risk increase (RRI) and relative risk reduction (RRR) methods refer to differences between two groups expressed as a proportion of the event rate of the control group. This is calculated using the following formula: $(EER - CER)/CER$ (see table 6.2). With the examples presented above (table 6.1), the RRI will be 2 $((3 - 1)/1 = 2)$, and the RRR will also be 2 $((150 - 50)/50 = 2)$. In order to get a percentage value, the total score can be multiplied by 100 as demonstrated by the following formula: $((EER - CER)/CER)*100$. Contrary to absolute risk methods, the relative risk method remains constant regardless of the size of the original event rate.

In order to communicate how much the medication will increase the risk of an adverse effect, the following statement may be provided to patients in which the relative terms can be expressed in the form of frequencies, probabilities or percentages: “compared to the placebo group, *2 times as many patients OR double the number of patients OR 200% more patients* will show an increase in the risk of adverse effect when taking the medication”. Since the example for RRR produces the same result, a similar statement could be used to provide RRR information about the benefits of taking the medication in comparison to the placebo group. Relative terms are commonly employed to present treatment benefits to patients with MS in current clinical practise within the UK (see appendix 11).

5.1.5 Numbers needed to harm and numbers needed to treat

Numbers needed to harm (NNH) and numbers needed to treat (NNT) refers to the average number of people who must be treated in the intervention group in comparison to the control group, in order for one patient to develop the risk or benefit. Both NNH and NNT are the reciprocal of the absolute method of communicating differences (i.e. the number one can be divided by the absolute method to obtain NNH and NNT). Thus, both NNH and NNT can be calculated using the formula: $1 / (\text{EER} - \text{CER})$ (see table 6.2), where EER and CER are the fractions of the EER and CER presented in table 6.1. With the example data from table 6.1, NNH will be 500 ($1 / (0.003 - 0.001) = 500$), and NNT will be 10 ($1 / (0.15 - 0.05) = 10$).

Both the NNH and NNT are usually expressed in the form of the average patients that would need to be treated at any certain point in time. Thus, the following statement may be used to express the NNH method or the risks between groups: “compared to the placebo group, 500 people would need to take the treatment for 1 person to show a risk of the adverse effect after 1 year”. Similarly, to communicate NNT (i.e. benefits) from differences between the intervention group and the placebo group, patients may be provided with the following statement: “compared to the placebo group, 10 people would need to take the treatment for 1 person to perceive a benefit in the disease symptom.”

Overall, it should be noted that the statements used to convey each of these methods are not standardised across studies (Covey, 2007). For this reason, the statements presented above do not represent the precise text, or indeed an exhaustive set of statements that may be used to communicate the differences between two groups.

In summary, the differences between the intervention group and control group of a clinical trial can be communicated using absolute terms, relative terms and numbers needed to harm or treat, all of which rely on different formulas to calculate these differences. The following section will compare studies that have looked at the

effectiveness of these methods primarily in non-clinical populations and clinical populations other than MS, due to a limited number of studies that have examined this effect with MS patients. It is expected that studies from other populations will be able to inform the best methods to improve understanding in MS patients, which consequently could be used to develop a theoretical framework of MS patient understanding.

6.1.2 Review of methods to communicate differences between groups in non-clinical populations

Some studies have assessed only individual methods of communicating risk or benefit differences between groups in non-clinical populations. In earlier studies, participants perceived the risk as higher when presented with differences of risks between two groups using relative terms in comparison to simple frequencies (Halpern et al., 1989; Stone, Yates, & Parker, 1994). These findings showed that relative terms could influence the choices made by non-clinical populations. However, given that frequencies on their own do not communicate differences between groups, the comparison of relative terms with frequencies does not imply the efficacy of relative terms as a method of communicating risk differences. Another study sought to evaluate the effectiveness of communicating differences of benefits between groups using a relative risk reduction method alone. Participants were randomly presented with one of six probabilities of experiencing a benefit after taking a hypothetical drug (Sorensen, Gyrd-Hansen, Kristiansen, Nexøe, & Nielsen, 2008). Participants in this study did not generally change their decision to take the drug depending on the magnitude of the benefit, indicating difficulty in discriminating between probabilities when expressed in relative terms. Interestingly, self-reported understanding of the relative terms was high (Sorensen et al., 2008). Together, these studies suggest that relative terms are difficult to comprehend, but without directly assessing understanding of differences communicated in relative terms.

Other studies examined only the numbers needed to treat method to communicate differences to non-clinical populations. Kristiansen, Gyrd-Hansen, Nexoe and Nielsen

(2002) randomly presented participants with different levels of benefits (i.e. delay in adverse effects) of a hypothetical drug using the numbers needed to treat method. The authors found that, irrespective of the probabilities of treatment benefits, 80% of participants consented to the hypothetical drug. From this, Kristiansen and colleagues (2002) concluded that people cannot comprehend benefits expressed using the numbers needed to treat method. One explanation for this effect was proposed by Halvorsen, Selmer and Kristiansen (2007), who suggested that the numbers needed to treat method could be misleading for medications which do not treat a disease, but rather offer a delay in an adverse effect. This is of particular importance for DMDs in MS, which cannot cure the disease but rather offers delays in disease progression and the rate of relapses (see section 1.2). To test this theory, Halvorsen and colleagues (2007) presented non-clinical populations with a hypothetical drug either in terms of numbers needed to treat, or in a statement which provided the length and duration of the delay in developing the adverse effect (e.g. “patients who take the drug therapy for 5 years will live about 2 months longer before they get a heart attack”). The benefits provided for both methods were equivalent. The study found that a greater number of participants chose to take the drug when the benefits were expressed in terms of numbers needed to treat, rather than in delay of an adverse effect. This implied that both methods were understood differently by participants in the study. However, only self-reported understanding was measured which was equally poor for both methods (Halvorsen et al., 2007). Overall, the findings imply that numbers needed to treat may be difficult for non-clinical populations to understand, but the effect of this method on objective understanding is unclear.

Studies that have directly compared methods to communicate differences have observed some consistent findings on understanding of treatment risk and benefit differences in non-clinical populations. In one study, Hembroff, Holmes-Rovner and Wills (2004) presented participants with hypothetical risks and benefits of a medication in

absolute and relative terms, and recorded the respondent's willingness to recommend the medication to a friend. The authors concluded that rational decisions based on risks and benefits were made when information was presented in absolute terms, signifying better understanding of absolute terms rather than relative terms. However, objective understanding was not recorded. In addition, the absolute terms in this study were presented using the 1-in-X ratio (e.g. 1 in 200 and 1 in 500), which as shown in Experiment 2, can significantly reduce understanding when compared to the N-in-N*X ratios (e.g. 4 in 1000 and 2 in 1000; see chapter 5). For this reason, it is not possible to deduce from this study whether differences in treatment choice were due to information presented in absolute terms or due to information presented in specific ratios (Hembroff et al., 2004). Therefore, the numerical formats within the methods of communicating differences between groups also need to be carefully considered during presentation.

A number of studies have manipulated numerical formats in the methods used to communicate group differences to non-clinical populations. Two studies expressed the baseline information (i.e. information about EER and CER which can be presented at the beginning of every method) in either frequencies or percentages (Bodemer et al., 2014; Covey, 2011). Since the relative method relies on using a format such as a percentage, providing the baseline information with the relative risk meant that formats could be easily manipulated. Covey (2011) specifically recorded participants' decisions for whether to take the medication. Although participants showed no differences in their treatment choice when presented with absolute and relative terms in any numerical format, both methods provided in frequencies induced greater rational decisions than those provided in percentages (Covey, 2011). In a subsequent experiment with absolute and relative terms presented only in frequencies, but with a wider range of probabilities of risks and benefits, Covey (2011) found that absolute terms increased rational decisions compared to relative terms. However, both these experiments did not include a rigorous

measure of understanding. On the other hand, Bodemer and colleagues (2014) explicitly measured objective understanding by asking participants to state the baseline risk of the treatment group (i.e. EER). Similar to findings by Covey (2011), majority of participants showed greater understanding of treatment risks and benefits when baseline information was presented in a frequency format (Bodemer et al., 2014). However, when baseline information was presented using percentages, absolute terms were shown to improve understanding compared to relative terms presented using percentages (Bodemer et al., 2014). Hence, whilst differences presented in absolute terms generally show improvements in understanding, adding baseline information in the correct numerical format could further improve understanding of differences between groups. This was further supported by Berry, Knapp and Raynor (2006) who found no differences in objective understanding of absolute risk, relative risk and numbers need to harm when baseline information was included, suggesting better understanding of the presence of baseline information. Note, however, that without the addition of baseline information, absolute terms showed a greater advantage in understanding (Berry et al., 2006). These findings support the need for adding baseline information to all methods, and are also consistent with findings from Experiment 1 which found that formatting numerical information as frequencies can improve understanding of treatment information (see chapter 4).

In sum, studies with non-clinical populations can inform the need to employ methods of expressing differences between two groups to improve MS patients' understanding. Although objective understanding was rarely measured in the reviewed studies, absolute methods showed improvements in rational decisions compared to relative terms and numbers needed to treat or harm. Baseline information provided with these methods also seemed to increase understanding, provided this was presented in formats that could be easily understood. The next section will focus on evaluating these

methods in clinical populations which represent the population more likely to make decisions based on treatment information.

6.1.3 Review of methods to communicate differences between groups in clinical populations

Many studies with clinical populations have evaluated methods to communicate differences in risks and benefits by assessing patients' choice of medications. For instance, two studies presented patients with equally efficacious hypothetical treatments in both absolute and relative terms (Forrow, Taylor, & Arnold, 1992; Malenka, Baron, Johansen, Wahrenberger, & Ross, 1993). The findings showed that patients were more likely to choose medications when presented using relative terms, insinuating differences in understanding risks and benefits presented in different methods. In a more recent study, Perneger and Agoritsas (2011) randomly presented hospitalised patients and physicians with hypothetical differences between drugs in either of the following conditions: absolute method framed positively, absolute method framed negatively, relative method framed negatively, or a combination of all of these methods. The authors presumed that the combination of all methods will provide the most information and would increase understanding the most, hence all other methods were compared with this condition. Both physicians and patients showed similar differences in the decision to take a drug depending on the condition. However, since the condition which combined all methods was not significantly different to the decisions based on information presented in absolute terms, the authors concluded that absolute terms were the least biased method of presenting treatment information (Perneger & Agoritsas, 2011). These findings and other similar studies with clinical populations have been grouped together in a range of reviews, and consistently show that information provided in relative terms is more likely to unreasonably persuade patients to choose a treatment (Covey, 2007; Edwards et al., 2001; Fagerlin et al., 2011; Waldron, van der Weijden, Ludt, Gallacher, & Elwyn, 2011), whereas medications presented with numbers needed to treat or harm were least likely to

be accepted (Waldron et al., 2011). Studies have additionally found that numbers needed to treat were least preferred by cardiovascular patients (Goodyear-Smith et al., 2008) and treatment adherence was improved when presenting information using absolute terms to another group of cardiovascular patients (Stovring, Gyrd-Hansen, Kristiansen, Nexoe, & Nielsen, 2008). In general, many studies with clinical populations show clear discrepancies in the methods to communicate differences on patients' decision to take a medication, but how well these methods are understood by patients cannot be conclusively established from these studies.

A number of studies have evaluated the methods of communicating differences on understanding of risk and benefit information in clinical populations. In one study, a randomised cross-sectional survey presented patients in outpatient clinics with benefits of two hypothetical drugs for a hypothetical disease (Sheridan, Pignone, & Lewis, 2003). Baseline information was presented to all patients for these drugs. Differences in benefits between these drugs were communicated in either of the three methods: relative risk reduction, absolute risk reduction and numbers needed to treat. A combination of all three methods was also given to one group of patients. Understanding was assessed by asking patients to calculate the benefits of only one drug or compare the benefits of both drugs. Sheridan and colleagues (2003) found that patients were least accurate at understanding the benefits of drugs when treatment information was provided using numbers needed to treat. A combination of all methods also made it difficult for patients to calculate benefits of two drugs. Thus, both absolute and relative risk reduction were shown to be the most effective method to improve understanding of the benefits of two drugs (Sheridan et al., 2003). In another randomised approach by O'Donoghue and colleagues (2014), patients who had been diagnosed with high cholesterol were provided with hypothetical information about drugs to target their condition using absolute or relative methods without baseline information. Numerical formats were also manipulated in this study, in

that absolute terms were presented in either frequency, percentages or a combination of the two, and relative terms were presented in frequency or a combination of frequency and percentages. Findings showed poor understanding of risks and benefits when presented in relative terms in frequency and the greatest understanding of absolute terms presented in a combination of frequency and percentages (O'Donoghue et al., 2014). The authors concluded that providing information using absolute terms and combining the numerical formats was a better method to improve understanding.

6.1.4 Review of methods to communicate differences between groups in MS patients

Only one study with MS patients evaluated the methods of communicating differences between groups. Using a pre-post design, this study examined the effects of providing treatment information using absolute risk methods as part of developing a larger educational intervention (Kasper et al., 2006). The study revealed that MS patients were unable to calculate differences in risks and benefits between groups when presented only in absolute terms. Understanding of information provided in absolute terms showed improvements when baseline information was present. However, these improvements were only apparent in a small number of patients, as the majority of MS patients were unable to answer the question altogether (Kasper et al., 2006). The authors concluded that since the MS patient sample also included PPMS patient groups (see section 1.1.3 for an overview of MS subtypes) who do not typically make decisions about DMDs, the difficulties in understanding the information could reflect a motivational bias in these patients rather than the method used to provide treatment information.

In summary, whilst studies with clinical samples can provide important information about the best method to communicate differences between groups to improve understanding in MS patients, there was immense heterogeneity amongst studies in the methods employed and the outcome assessments. Reviews also indicate that there are large disparities between how one method is presented to patients across studies (Akl

et al., 2011; Covey, 2007; Zipkin et al., 2014). Regardless, the current evidence seems to show a trend towards absolute terms as the most effective method to improve understanding. Findings also suggest that adding baseline information to any method can be beneficial for understanding the information. However, the study directly conducted with MS patients, shows unclear findings about the best methods that can improve MS patients' understanding (see figure 6.1 for theoretical framework of MS patients' understanding based on this review).

6.1.5 Patient understanding and decisional conflict

Patients' understanding of medication information can have an impact on how conflicted they feel about making a treatment decision (Janis & Mann, 1977; O'Connor, 1995) (see section 4.1.5). It is evident from the above reviewed studies that the methods of communicating differences between groups can impact the decision to choose a treatment by non-clinical and patient populations (Covey, 2011; Fagerlin et al., 2011). However, the relationship between patients' understanding of these methods and the conflict in their decisions is unclear.

6.1.6 Patient understanding and patient characteristics

The ability to understand accurately the differences between intervention and control group of clinical trials may also be moderated by factors other than the methods that can be used to communicate these differences.

6.1.6.1 Numerical reasoning, health literacy and premorbid IQ

Numeracy skills have shown to mediate understanding of particular methods of communicating differences between groups. Sheridan and colleagues (2003) found that correct responses to information displayed in relative terms were as little as 5.8% for low numerate individuals. However, individuals with better numeracy skills were able to respond correctly to 40% of the questions. Likewise, individuals with low levels of numeracy showed the least understanding of medication information presented in relative

terms in another study (Bodemer et al., 2014). To note, the effect of numeracy skills on understanding of differences between groups disappeared on provision of baseline information for all methods (Bodemer et al., 2014). From these findings, it is expected that numeracy will play a role in MS patients' understanding of treatment information when differences between groups are communicated using different methods.

No studies explored the relationship between health literacy and IQ on understanding of treatment differences based on different methods to communicating these differences.

6.1.6.2 Symptoms of MS

MS patients with cognitive and affective symptoms may be particularly susceptible to poor understanding when differences between groups in clinical trials are presented using complex methods. These symptoms include: fatigue, depression, anxiety, deficits in information processing-speed and impairments with working memory (see section 1.1.2 for overview of MS patient symptoms).

6.1.7 Research questions and hypothesis

The following study addressed two specific questions, which were represented in the form of a theoretical framework (see figure 6.1). First, which methods of communicating differences between groups (absolute risk reduction/increase, relative risk reduction/increase, and numbers needed to treat/harm), with or without baseline information, could maximise understanding of risk and benefit information in MS patients? Second, what is the relationship between MS patients' understanding when presented in these methods and patients' conflict in treatment decisions? Additional exploratory questions attempted to address how patients' numerical reasoning, health literacy, premorbid IQ and symptoms of MS could impact MS patients' understanding of information communicated in different methods?

Hypotheses for the following study was derived from previous literature and were as follows:

- (v) Baseline information added to all methods will maximise understanding compared to methods without baseline information;
- (vi) Absolute risk reduction and absolute risk increase would maximise understanding in comparison to other methods, without baseline information;
- (vii) Numbers needed to treat and numbers needed to harm would result in the least understanding in comparison to other methods, without baseline information;
- (viii) Greater understanding of information will reduce decisional conflict in MS patients;
- (ix) Numerical reasoning will be positively related with understanding of information.

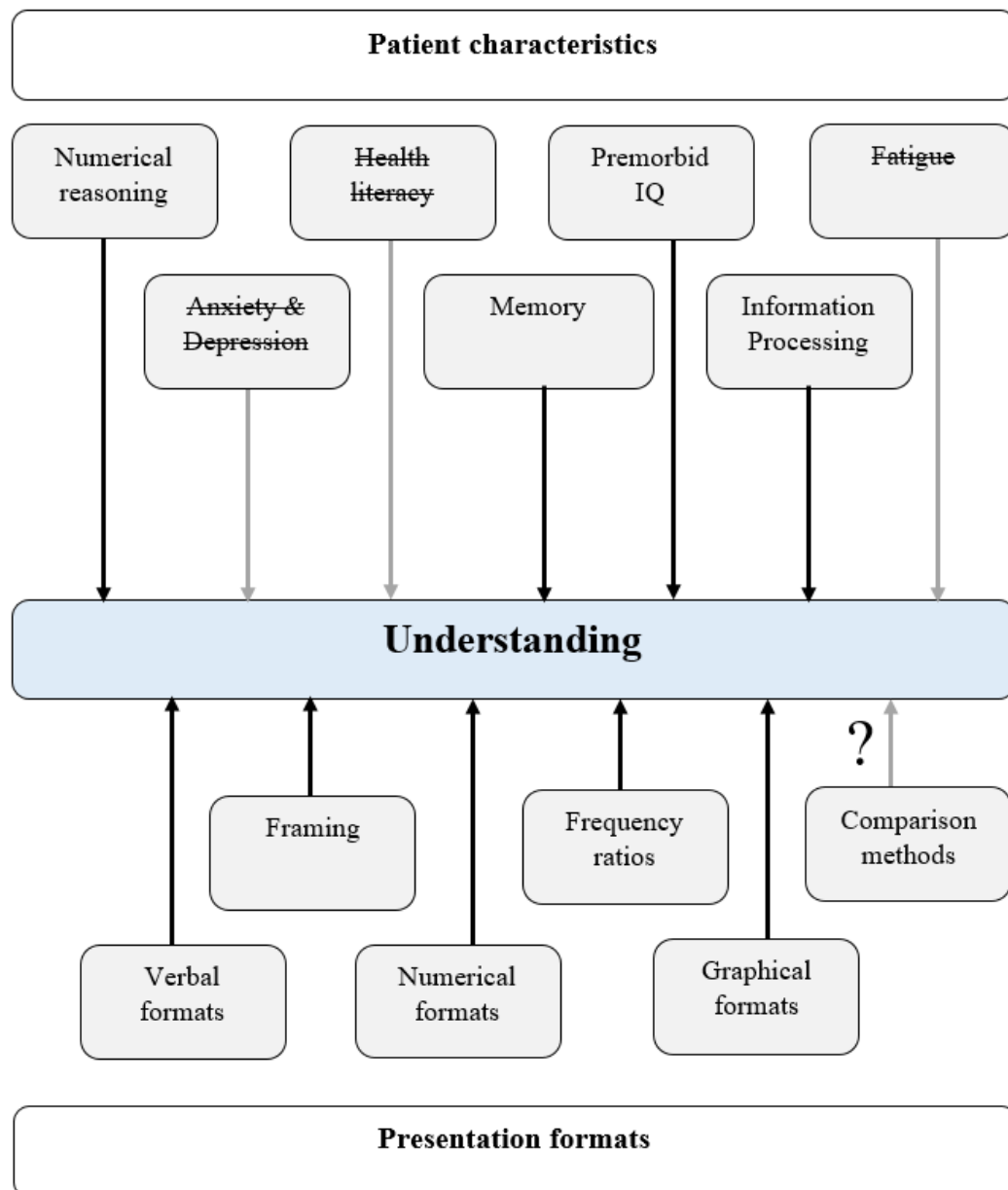


Figure 6.1 Theoretical framework 5: Factors affecting MS patients' understanding of treatment risks and benefits

Key: Black arrows, significant effect; Grey arrows, no relationship; Question, Untested factors; arrows do not signify causation

6.2 Experiment 3 methodology

6.2.1 Participants

All participants in the current experiment were the same as participants who had taken part in experiment 2. The inclusion and criteria also remained the same for these participants (see section 4.2.1).

6.2.2 Materials and design

This was a cross-sectional within-subject experiment designed to assess patients' understanding and decisional conflict for different methods of communicating differences between two groups.

One hypothetical disease was presented in the experiment, for which risk and benefit information was provided for two hypothetical treatments. The name and symptoms of the disease were new in the current experiment, but mimicked the progressive nature of MS, similar to experiments 1 and 2 (see appendix 17 for the hypothetical medical disease). Two hypothetical treatments were provided to patients for this hypothetical disease. Treatment names and the associated risks and benefits of the treatments were also new in the current experiment, but were checked by a small survey sample as discussed in Experiment 1 (see section 4.2.2). The risk-benefit profiles of the treatments were also similar to those provided to patients in Experiments 1 and 2 (i.e. one treatment offered high risks and high benefits, and the other treatment offered low risks and low benefits).

All three methods of communicating differences between two groups (absolute terms, relative terms and numbers needed to treat or harm) were presented to patients, either with or without baseline information; hence, there was a total of six possible methods to communicate differences between the intervention and control group. Baseline information was provided in frequencies presented in the N-in-N*X ratio, which are shown to be the best format for presenting quantitative information to MS patients

(see chapters 1 and 2). The order of all six methods to communicate differences between groups was initially randomised across the two hypothetical treatments (see table 6.3). To further reduce any effects of order, the treatments were counterbalanced between patients. Each method either communicated differences between the intervention group or control group, for either the minor risk, adverse risk or benefit of the hypothetical treatment over 1 year, 2 years and 5 years of taking the treatment (see appendix 18 for example of communication methods for one treatment).

Table 6.3 Order of methods to communicate differences between groups in Experiment 3

Treatment	Outcome	Method of communicating differences
Treatment 1	Adverse risk	Absolute risk– without baseline
Treatment 1	Minor risk	Numbers needed to harm – with baseline
Treatment 1	Benefit	Numbers needed to treat – without baseline
Treatment 2	Adverse risk	Relative risk – with baseline
Treatment 2	Minor risk	Relative risk – without baseline
Treatment 2	Benefit	Absolute risk – with baseline

Treatment 1 was named Triptyte; Treatment 2 was named Frodytin

The main outcome measures in the experiment were patients' understanding and patients' conflict in their treatment decisions. These measures were collected in the same way as Experiment 2. However, given the fewer number of methods that were compared in the current experiment, treatments only included one minor risk, one adverse risk and one benefit. Maximum score for each treatment outcome was 6 points and therefore total score for each treatment was 18 points. Maximum scores for understanding across both treatments was therefore 36 points (see appendix 18 for example of understanding questions). All other materials provided to patients throughout the experiment were the same as those used in Experiments 1 and 2, and include measures assessing: numerical reasoning, health literacy, premorbid IQ and the cognitive and affective symptoms of MS.

6.2.3 Procedure

The procedure for recruiting interested patients from the two hospital clinics was the same as discussed in Experiment 1 (see section 4.2.3). Following consent, an appointment was made with patients to take part in the study. The study was conducted either at the clinics or at the patient's home, depending on patients' preference. The study took approximately 2 hours to complete and was conducted face-to-face using offline materials only.

Initially, patients were presented with the visual acuity scale to ensure they were eligible to view the remaining study (see section 4.2.1). If eligible to continue, patients were asked demographic questions and assessed on the disability status scale. Next, patient characteristics were measured in the following order: health literacy, numerical reasoning, depression and anxiety, fatigue and premorbid IQ. All patients were then shown information about one hypothetical chronic medical disease followed by two hypothetical treatments. Comprehension questions to assess understanding were provided after each treatment outcome. Patients were also required to make their treatment choice and complete the DCS measure after viewing both treatments. Finally, the BICAMS measure was conducted with patients at the end of the study. Note, however, that since this experiment was conducted alongside Experiment 2, all measures (aside from the main task) were only measured once. Both Experiment 2 and the current experiment were conducted in alternating order between patients.

6.2.4 Sample size

Sample size was calculated to detect an effect on MS patients' understanding of treatment risks and benefits. The calculation was similar to that given in Experiment 1 (see section 4.2.4) and required a minimum sample of 45 MS patients.

6.2.5 Statistical analysis

All statistical analysis were carried out using SPSS 21. Means and standard deviations were provided for all continuous data. Maximum scores were also given for all measures in the experiment. A test of normality was conducted for the understanding outcome measure for each format using the Shapiro-Wilks test. The assumption of normality was significantly violated for all numerical ratios and framing ($p < .001$) and therefore a nonparametric Friedman analysis of variance was conducted. Where the Friedman test was significant, pairwise comparisons were conducted by using the nonparametric Wilcoxon Signed Ranks test. Bonferroni corrections were applied for multiple comparisons. Effect sizes are calculated for all pairwise comparisons by dividing the z score by the square root of total number of observations, based on Rosenthal's formula (Rosenthal, 1994); where, 0.1, 0.3 and 0.5 equates to small, medium and large effect sizes, respectively. For the purpose of the analysis, several methods were sometimes collapsed into one average understanding score.

A bivariate Pearson's product moment correlation was further computed to assess the relationship between patient understanding and the standardised scores of the decisional conflict scale, including all subscales. Bivariate Pearson's product-moment correlations were also computed to assess the relationship between understanding and raw scores on measures of numerical reasoning, health literacy, premorbid IQ and symptoms of MS. Due to multiple correlations, a stringent alpha of $p < .01$ was applied and accepted as significant.

6.3 Results

6.3.1 Patient demographics

Since the present experiment contains the same sample as Experiment 2, all patient demographics were the same as those presented in Experiment 2 (see section 5.3.1).

6.3.2 The effect of methods to communicate differences between groups on patients' understanding

There was a statistically significant difference in the methods to communicate clinical trial data (absolute terms, relative terms, numbers needed to treat/harm) on patients' understanding, $X^2(2) = 39.688$, $p < .001$. Pairwise comparisons were conducted to statistically compare the means for absolute terms ($M=3.99$, $SD=.93$), relative terms ($M=2.93$, $SD=.91$) and numbers needed to treat/harm ($M=2.89$, $SD=.88$). Understanding was greater for absolute terms compared to relative terms ($z=-4.800$, $r=0.51$, $p < .001$) and numbers needed to treat/harm ($z=-5.058$, $r=0.53$, $p < .001$). There was no significant difference between relative terms and numbers needed to treat/harm ($z=-.620$, $p=.535$).

There was also a statistically significant difference between baseline added to all methods and no baseline information on all methods, $X^2(1) = 45.000$, $p < .001$. According to mean scores, understanding was greater for baseline information on all methods ($M=5.04$, $SD=.96$) compared to no baseline information on all methods ($M=1.49$, $SD=.74$, $z=-5.856$, $r=0.62$).

6.3.3 Patient understanding and decisional conflict

A bivariate Pearson product-moment correlation showed no significant correlation between patients' understanding and the total decisional conflict score. There were also no significant correlations between understanding of treatment information and any other DCS subscales (see table 6.4).

Table 6.4 Correlations between patient understanding and decisional conflict

	Max score	Mean	SD	Correlation
Total understanding	36	19.62	4.22	
DCS informed	100	30.74	21.31	.100
DCS values	100	33.52	24.07	-.344*
DCS support	100	30.19	20.97	-.033
DCS uncertainty	100	57.04	26.35	-.001
DCS effective	100	60.56	33.40	-.163
DCS total score	100	39.44	19.70.	-.131

* = indicates significance at the $p < .05$ level; ** at $p < .01$ level; *** at $p < .001$ level; DCS, Decisional conflict scale

6.3.4 Patient understanding and patient characteristics

Patients were assessed for numerical reasoning skills, health literacy, premorbid IQ and MS symptoms in the current experiment. The number of patients impaired on each of these measures are the same as discussed in Experiment 2 (see table 5.4). A bivariate Pearson product-moment correlation coefficient was computed to assess the relationship between treatment understanding scores and patient characteristics. Means, standard deviations and correlations for all factors are presented below (see table 6.5).

There was a significant correlation between understanding of treatment information and numerical reasoning ($r = .517$, $p < .001$), premorbid IQ ($r = .434$, $p < .001$), information processing speed ($r = .439$, $p < .01$) and verbal memory ($r = .409$, $p < .01$). There was no significant relationship between understanding of treatment information with health literacy, anxiety, depression, fatigue and visual memory.

Table 6.5 Correlations between patient understanding and patient characteristics

Patient characteristics	Max score	Mean	SD	Correlation
Total understanding	36	19.62	4.22	
Numerical reasoning	25	16.36	3.80	.517***
Health literacy	8	7.42	1.32	.257
Anxiety	21	6.27	3.98	-.348*
Depression	21	4.11	3.69	-.257
Fatigue	63	44.00	13.47	-.123
Premorbid IQ	50	36.69	8.46	.434***
Information processing speed	110	56.62	12.62	.439**
Verbal memory	80	49.07	12.43	.409**
Visual memory	36	21.16	6.46	.287

* = indicates significance at $p < .05$ level, ** at $p < .01$ level; *** at $p < .001$ level; correlations in bold accepted as significant due to multiple correlations

6.4 Discussion

The risk and benefit profiles of DMDs can be derived from clinical trials by comparing the risks and benefits patients experience when taking the DMD, with patients taking a placebo or an existing treatment (e.g. Braune et al., 2015; Chahin et al., 2015; Fogarty et al., 2016; Maruszczak et al., 2015; McFarland, 2009; Miller et al., 2014). Risk and benefit differences between groups in clinical trials should be effectively communicated to MS patients in order for patients to make informed decisions about DMDs. There are a number of methods that can be used to communicate differences between two groups such as those in clinical trials, including absolute terms, relative terms and numbers needed to treat or harm. The current experiment confirmed that certain methods to communicate group differences from clinical trials can impact MS patients' understanding of treatment risk and benefit information.

In support of our hypothesis, communicating differences using absolute terms significantly improved understanding of treatment information compared to relative terms

and numbers needed to treat irrespective of the baseline information. This is consistent with previous studies of non-clinical and clinical populations which found that individuals were more likely to make rational decisions (Covey, 2011; Hembroff et al., 2004) and have greater understanding (Berry et al., 2006; Bodemer et al., 2014) of treatment information presented using absolute methods. The advantage of using absolute terms was particularly apparent in the absence of baseline information or when baseline information was provided using percentages (Berry et al., 2006; Bodemer et al., 2014). Given that Experiment 1 shows that percentages can often lead to errors in understanding by MS patients (see chapter 4), these findings suggest that absolute methods can be beneficial when baseline information is misunderstood or missing.

MS patients showed the least understanding of treatment information presented in relative terms and numbers needed to treat or harm in the current experiment. One explanation for why MS patients may have had difficulty in understanding relative terms could be because MS patients may have misinterpreted the group differences expressed in relative terms as absolute differences. This was shown to be the case in a recent study carried out by Bodemer and colleagues (2014) with non-clinical populations. These misinterpretations are likely to lead to large errors in comprehension, considering that differences expressed in relative terms are substantially larger and more impressive than the same differences presented using absolute methods (Barratt et al., 2005). This also explains why many patients choose to take a medication when the benefits of a treatment derived from differences between two groups are expressed using the relative risk reduction method (Covey, 2007; Edwards & Elwyn, 2001; Fagerlin et al., 2011; Forrow et al., 1992; Malenka et al., 1993; Waldron et al., 2011). This is especially problematic for MS patients, given that relative terms are commonly employed to display DMD benefits to patients in current clinical practices within the UK (see appendix 11).

Moreover, although the method of numbers needed to treat or harm has been recommended for use in healthcare due to its reciprocal nature with the absolute method (Barratt et al., 2005) and due to patients making conservative decisions for treatments with this method compared to relative terms (Waldron et al., 2011), studies with non-clinical populations has also shown that individuals are not able to distinguish between treatments when expressed as numbers needed to treat (Kristiansen et al., 2002). One explanation is that numbers needed to treat is not appropriate for medications that cannot treat a disease but rather offer a delay in progression of the disease. This is true for DMDs which are not able to treat MS but can offer a delay in relapses and progression of disability (see section 1.2 for reviews about DMD benefits). Thus, in one study, when equivalent numerical data was provided to non-clinical populations by stating the delay in adverse effect rather than simply stating the numbers needed to treat, participants' decision to choose a particular treatment was affected (Halvorsen et al., 2007). However, since this experiment did not assess participants' understanding, it is not possible to determine whether MS patients' understanding could be improved by changing numbers needed to treat to numbers needed to delay. Another explanation is that numbers needed to treat or harm is essentially written in the form 1-in-X which in itself is difficult to comprehend (Bodemer et al., 2014; Sheridan et al., 2003). Poor understanding of information presented using 1-in-X has been demonstrated by studies with non-clinical and clinical population groups, and was also shown in Experiment 2 (see chapter 5), further providing support to this explanation.

The effect of baseline information on MS patients' understanding was also explored in the current experiment. The presentation format of the baseline information was deliberately chosen as frequencies using the N-in-N*X ratio in light of findings from Experiments 1 and 2, and that of previous findings which show an effect on understanding of baseline information depending on different formats (Akl et al., 2011;

Ancker et al., 2009; Garcia-Retamero & Hoffrage, 2013; Knapp et al., 2009; Knapp et al., 2015). In support of our hypothesis, the addition of baseline information with the different methods significantly improved understanding of treatment information in MS patients. Adding baseline information could be especially important when absolute terms are used to communicate differences between groups, since absolute risk differences can vary depending on the size of the original event rate. Therefore, to avoid presenting patients with misleading information when event rates differs between clinical trials, baseline information should ideally be included at all times.

When understanding of medication information was compared with patients' conflict about their treatment decision, no significant relationship was observed. These results mimic our previous experiment (see chapters 4 and 5). Thus according to the present experiment, improving patients' understanding did not reliably reduce conflict patients experience in their treatment decision based on different methods of communicating differences. The symptoms of MS and individual characteristics of patients were also compared with treatment understanding scores in the present experiment. As hypothesised, numerical reasoning showed a significant positive relationship with understanding of treatment risk and benefit information. This is supported by previous studies of clinical and non-clinical populations which show a consistent advantage of higher numeracy on understanding the information about medications (Bodemer et al., 2014; Galesic & Garcia-Retamero, 2015; Peters, 2008). Interestingly, significant relationships were also observed with measures of premorbid IQ, information processing speed, verbal memory, depression, anxiety and fatigue. This indicates that patients with these characteristics are more susceptible to misunderstanding when differences between clinical trial groups are not communicated clearly. It is likely that when these differences are communicated using absolute terms with baseline

information, according to the findings from the current experiment, the most vulnerable patient groups will show improvements in understanding the treatment information.

Although the present experiment adds to the pool of findings about the impact of different methods to communicate differences between groups, there are some limitations present. First, not all methods of communicating differences were explored in this experiment. For instance, the method designed to present numbers needed to delay an adverse effect proposed by Halvorsen et al (2007) was not assessed in the present experiment. However, given that this method also provides a similar 1-in-X ratio as provided in the numbers needed to treat method, it is unlikely that this method could have improved understanding of treatment information in MS patients based on the findings from Experiment 2. Second, understanding of treatment information when all methods were combined was not examined in the current experiment. However, a previous study that did combine these methods found no significant improvements in understanding of treatment risks and benefits (Perneger & Agoritsas, 2011).

6.4.1 Conclusion

Despite the limitations, findings from the current experiment indicate that methods to communicate differences between groups in a clinical trial can significantly influence MS patients' understanding of treatment risks and benefits. The present findings also suggest that there is no relationship between patients' objective understanding and their decisional conflict when treatment information from clinical trials are communicated using different methods. Having established these effects, the theoretical framework based on the literature review was updated (see figure 6.2).

With the evidence obtained from this experiment, some recommendations may be made on ideal communication methods when providing DMD risks and benefits from clinical trials to MS patients. For instance, it is recommended that baseline information using frequencies be provided with any form of method. In addition, the differences of

risks or benefits from the intervention and control group from clinical trial information should be communicated using absolute terms. Relative terms and numbers needed to treat or harm should be avoided. Patients with poor numerical skills, poor IQ and cognitive impairments may further benefit from additional support when information is provided about clinical trial data.

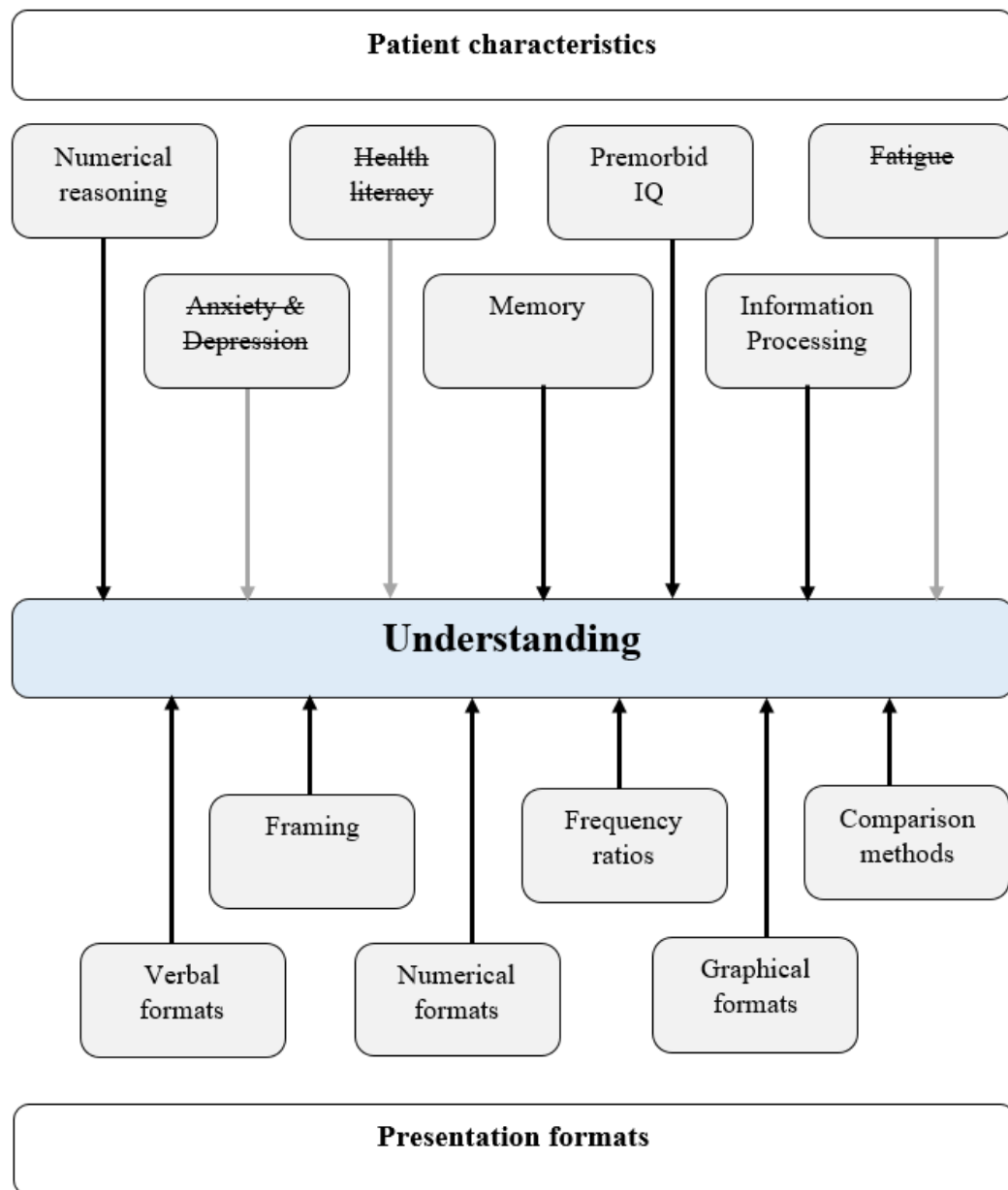


Figure 6.2 Theoretical framework 6: Factors affecting MS patients' understanding of treatment risks and benefits

Key: Black arrows, significant effect; Grey arrows, no relationship; Question, Untested factors; arrows do not signify causation

Chapter 7: A crossover randomised controlled trial to evaluate the BRIMMS protocol

7.1 Introduction

Within patient-centred healthcare, it is recommended that treatment decisions between health professionals and patients be based on shared decision-making (see section 1.3 for review of shared decision-making). A prerequisite for effective shared decision-making is that patients are fully informed about all available treatment options and clearly understand the minor risks, adverse risks and benefits associated with the treatments (Barry & Edgman-Levitan, 2012; Charles et al., 1997, 1999; Godolphin, 2009). However, there is evidence that MS patients do not satisfactorily understand the complex risk and benefit profiles of disease-modifying drugs (DMDs) they receive during standard healthcare; DMD risks are generally underestimated and DMD benefits are generally overestimated by MS patients (Reen et al., 2017). MS patients in the UK also report poor understanding of DMD risks and benefits (see chapter 3 for surveys with MS patients). Patients with poor numerical reasoning, low premorbid IQ and those displaying symptoms of cognitive impairments in MS are particularly susceptible to misunderstanding treatment risks and benefits (see Experiments 1, 2 and 3, and updated theoretical framework presented in figure 6.2). Misunderstanding treatment information can likely affect treatment decisions and lead to treatment discontinuation, as risks and benefits of the chosen DMD may not reflect preferred levels of risks and benefits patients are willing to take (Menzin et al., 2013; Vangeli et al., 2015). This may consequently affect adherence to treatments in MS, given that DMDs need to be administered for long durations to show reduction in progression of disease (see section 1.2 for review about DMDs). Thus, it is crucial that MS patients have greater understanding about the risks and benefits of DMDs when making treatment decisions during standard healthcare.

Interventions have been designed to improve MS patients' understanding of DMD risks and benefits, and show moderate success (Reen et al., 2017a). However, the design and implementation of these interventions vary considerably between studies. In particular, the methods used to present treatment risk and benefit information differs between these interventions, and these are rarely incorporated with direct evidence from MS patients (Reen et al., 2017a). Given that the methods used to present treatment risks and benefits can significantly affect understanding in MS patients (see Experiments 1, 2 and 3), interventions designed for MS patients should only present treatment information using methods that best support understanding in MS patients.

7.1.1 Methods to improve MS patients' understanding and reduce conflict in treatment decisions

Experiments 1, 2 and 3 of the current thesis were designed to evaluate the best methods of presenting treatment risk and benefit information to MS patients in order to improve understanding. Experiment 1 showed that MS patients presented with treatment information in frequencies were better able to understand the information in comparison to information presented in percentages or verbal terms. Experiment 1 also demonstrated that presenting treatment information in bar charts or line graphs was able to improve MS patients' understanding in comparison to pictographs or pie charts. In particular, information in horizontal bar charts was better understood compared with vertical bar charts. Findings from Experiment 2 showed that frequencies were better understood by MS patients when information was presented in the N-in-N*X ratio (e.g. 20 in 1000), instead of the 1-in-X ratio (e.g. 1 in 50). Experiment 3 found that MS patients were better able to understand the differences between two groups (i.e. differences between intervention and control group of a clinical trial) when communicated using absolute terms, in comparison to relative terms or numbers needed to treat or harm. These findings are shown in an integrated theoretical framework (see figure 6.2).

In short, these experiments were designed to find the best methods to present treatment risks and benefits to MS patients. It was expected that integrating the most effective methods of presenting treatment risk and benefit information into an intervention could maximise MS patients' understanding of DMD risks and benefits. These experiments, however, did not show any relationship between patients' understanding of treatment information presented in different formats and conflict in their treatment decisions. Despite this, several studies find that interventions providing treatment information to non-MS patients are able to both improve understanding and reduce decisional conflict (e.g. Arterburn et al., 2011; Evans et al., 2010; Nassar, Roberts, Raynes-Greenow, Barratt, & Peat, 2007; Wong, Thornton, Gbolade, & Bekker, 2006). Thus, it is conceivable that an intervention combining all effective presentation methods could also reduce MS patients' conflict in treatment decisions.

The current experiment was designed to evaluate an intervention to provide treatment risks and benefits to MS patients. Considering that MS patients primarily receive treatment information from neurologists and nurses (Bishop, Frain, Espinosa, & Stenhoff, 2009; Hepworth & Harrison, 2004; Marrie, Salter, Tyry, Fox, & Cutter, 2013; Matti, McCarl, Klaer, Keane, & Chen, 2010; Somerset, Campbell, Sharp, & Peters, 2001; see also MS patient surveys in chapter 3), the intervention was primarily designed for use in consultations by health professionals. For this reason, the current experiment sought to compare this intervention with standard consultations that MS patients currently receive using a randomised controlled trial with a crossover design.

7.1.2 Randomised controlled trial with a crossover design

A crossover design was employed in the current randomised controlled trial (RCT). A crossover design refers to a trial where every participant receives all possible conditions such that each participant serves as his/her own control (Wellek & Blettner, 2012). For instance, after a participant receives the first condition (in period 1) and all

relevant outcome measures have been recorded, they are ‘crossed-over’ to the next condition (in period 2) until they have received all possible conditions (Wellek & Blettner, 2012). The randomisation then occurs for the order or sequence in which the conditions are given to each participant (Wang, Wang, & Gong, 2009; Wellek & Blettner, 2012). For example, in a crossover study with an intervention condition and a control condition, all patients in the study would experience both the intervention and control conditions. However, the randomisation would occur for the sequence in which the interventions and control will be given: patients could be randomised to a sequence where the intervention is given first (period 1) followed by the control (period 2), or patients may be randomised to the sequence where the control is given first (period 1) followed by the intervention (period 2). This design can be referred to as a 2-condition 2-period design and is demonstrated by figure 7.1 below. To note, crossover designs can also consist of more than 2 conditions over more than 2 periods.

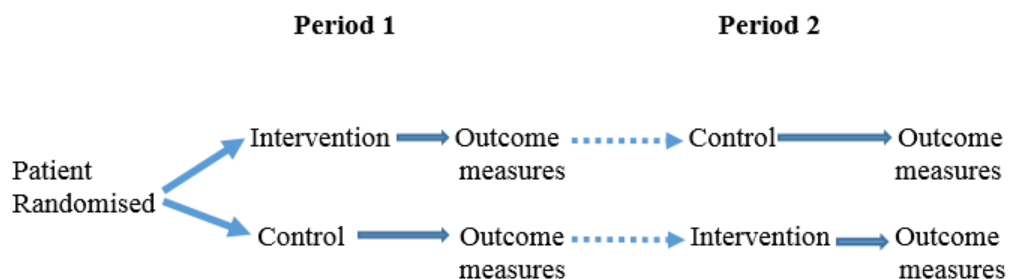


Figure 7.1: Example of randomisation in 2-condition 2 -period crossover design

Crossover designs should only be applied in medical diseases where the first condition cannot completely change the disease course (for example, by curing the disease) prior to subsequent conditions. Thus, crossover designs are better suited to chronic medical diseases such as MS. In addition, any interaction between period and conditions, termed as the carry-over effect, must be minimised during the design of the

study or at least accounted for in the analysis to effectively use the crossover design (Senn, 2002). One way to prevent any carry-over effects is to ensure the gap between subsequent conditions is sufficient, such that one condition given to participants does not affect any subsequent conditions given to participants (Senn, 2002). Alternatively, all conditions should be kept as different as possible to all other conditions in the RCT (Senn, 2002).

There are many reasons why a crossover trial is preferable to the most commonly used parallel group design RCT, in which participants are separated into independent groups and each group only receives one condition (Senn, 2002). First, confounding variables that occur between participants in a parallel group design are eliminated in a crossover design, as each participant receives all conditions (Senn, 2002; Wellek & Blettner, 2012). Because the error between participants is reduced, fewer number of observations are needed in a crossover design in order to achieve the same precision and statistical power as a parallel group design (Senn, 2002). For this reason, a fewer number of participants are needed in a crossover trial in order to obtain the same number of observations as a parallel group design (Senn, 2002; Wellek & Blettner, 2012).

Given that the current experiment met the basic criteria of a crossover trial (i.e. chronic disease and minimal carry-over effects as different treatment information was used in each condition), and due to a limited number of MS patients available for recruitment, a crossover RCT was considered the most suitable design to compare the intervention with standard consultations.

7.1.3 Research question and hypothesis

A protocol for providing benefit and risk information for medication in Multiple Sclerosis (BRIMMS) was developed for the present experiment, to provide treatment risks and benefits using the best presentation methods based on findings from Experiments 1, 2 and 3. All presentation methods had been previously tested in a written

form, and thus a written BRIMMS protocol was developed. The BRIMMS protocol was then compared with medication information as presented in a standard consultation in the UK. Since standard consultations are usually conducted aurally with patients, the BRIMMS protocol was also designed for aural presentation to allow for direct comparisons between the aural standard consultation with the BRIMMS protocol. Further, in order to examine the efficacy of the BRIMMS protocol developed in a written format, a direct comparison was also made with a written version of a standard consultation.

The current experiment addressed two main questions. First, could the BRIMMS protocol (either written or aural) improve patients' understanding compared to standard consultations (either written or aural)? Second, could the BRIMMS protocol (either written or aural) reduce patients' conflict in their treatment decisions compared to standard consultations (either written or aural)? Additional exploratory questions attempted to address how understanding was associated with patients' numerical reasoning, health literacy, premorbid IQ and MS symptoms?

The hypothesis from this study was derived from Experiments 1, 2 and 3 and the previously reviewed literature in this thesis, and were as follows:

- (i) The BRIMMS protocol (written and aural) would improve patients' understanding of treatment risks and benefits compared to standard consultation (written and aural);
- (ii) The BRIMMS protocol (written and aural) would reduce patients' conflict in treatment decisions compared to standard consultation (written and aural);
- (iii) The BRIMMS protocol (written and aural) would be positively rated compared to standard consultation (written and aural).

7.2 Experiment 4 methodology

7.2.1 Participants

A total of 24 RRMS patients were recruited in this experiment. All patients had not previously taken part in previous experiments of this thesis. The recruitment location, and inclusion and exclusion criteria for eligible patients were the same as those discussed elsewhere (see section 4.2.1).

7.2.2 Materials and design

The present experiment was a single-blinded crossover randomised controlled trial (RCT). In total, four conditions were evaluated in the present experiment, defined by the four possible combinations of the factors ‘type of consultation’ (standard or BRIMMS) and ‘method of consultation’ (written or aural). Therefore, this was a 4-condition 4-period design. This means that MS patients were assigned to all four conditions over four subsequent periods of time (see figure 7.1 for example of randomisation for 2-condition 2-period design). The sequences that determined the order in which MS patients received all four conditions were balanced by using Latin squares containing 4 sequences in each ‘square’. Latin squares are balanced in that every condition is represented in every period with the same frequency throughout the square, as each condition within a square is represented once in each column of the square and once in each row of the square (Senn, 2002). To balance the sequences even further in the present experiment, the Latin squares used for the crossover design had the property that every condition followed every other condition once in each square. Latin squares with these properties are also termed as Williams squares (Senn, 2002). In total, 6 William squares were used in the present experiment with 4 sequences in each set; i.e. all 24 possible sequences were included in the present experiment (see appendix 19).

All patients were allocated randomly to each of the 24 sequences in the experiment using a random sequence generator. Random allocation was conducted

independently by the supervisor (DL) who had no role in data collection. The random order was given to the data collector (GR) using sealed envelopes. The experiment was a single-blind study as patients were blind to both the condition they received and the order in which they received the conditions.

Patients were presented with information about one hypothetical disease throughout the experiment. Similar to previous studies (see section 4.2.2), the disease was described as progressive and a list of symptoms were presented. A name was also provided for the hypothetical disease (see appendix 20 for disease information given to patients). Throughout the experiment, patients were presented with hypothetical treatments for the disease. Specifically, two minor risks, one adverse risk and one benefit was provided to patients for each hypothetical treatment. All hypothetical treatment risks (minor and adverse) and benefits mimicked DMD risk-benefit profiles as closely as possible, as previously done in Experiments 1, 2 and 3 (see section 4.2.2). To increase the validity of the experiment, all risks were feasible and could be associated with medications. The disease and treatment names were assigned by the experimenter, and the level of treatment risks were checked by a small survey sample prior to beginning the experiment, as discussed in Experiment 1 (see section 4.2.2). The treatment benefits were stated as the delay in progression of the hypothetical disease, which is similar to the benefits offered by all DMDs in MS. Levels of risks and benefits approximated those observed in MS DMDs.

For the purpose of this experiment, a ‘set’ of two hypothetical treatments were always presented together. There were four sets in total, each with two different treatments. In order to decide the set of treatments that would be presented in each consultation (i.e. BRIMMS written, BRIMMS aural, standard written and standard aural), the order of sets was randomised for all 24 sequences prior to beginning the experiment. That is, treatments in one set could be given to patients for either of the BRIMMS

protocol or either of the standard consultations. The order that each treatment will be presented within the set was further randomised. What remained common between sets was that one medication always presented patients with high risks and high benefits, whereas the other treatment yielded low risks but in return for lower benefits. These different risk-benefit profiles were chosen to mimic the choices that may be faced by some MS patients during treatment decision-making: choosing between a first-line DMD (low risk and low benefit), or second-line DMD (high risk and high benefit) (see section 1.2 for review about DMDs). After presentation of each set, patients were asked to make a treatment decision (i.e. either choose one of the two hypothetical treatments, choose neither option, or state that they were unsure). Since all patients were presented with all four sets of treatments, patients were required to make four different treatment decisions.

7.2.2.1 BRIMMS protocol

The intervention given to MS patients in the current RCT was the BRIMMS protocol. This protocol was developed by combining the best methods of presenting treatment information based on findings from Experiments 1 to 3, as presented in a theoretical framework (see figure 6.2).

The content of the intervention mimicked real DMD information as closely as possible. MS patients were presented with risks and benefit information for two hypothetical treatments, based on the set that was assigned to the BRIMMS consultation. Treatments were always presented in the order of benefits of taking the drug, minor risks of taking the drug and adverse risks of taking the drug. To further mimic real DMD information, all risks and benefits were provided for both short-term (1 year and 2 year) and long-term (5 years) outcomes. A hypothetical clinical trial scenario was provided to patients to communicate the treatment benefits, and patients were provided with differences between the intervention group (taking a treatment) and a placebo group (taking no treatment) from this clinical trial. This was done to mimic the manner in which

DMD benefit information is provided to patients during standard healthcare. Although real DMD clinical trials also increasingly compare the intervention group taking the treatment with patients taking other active DMDs as the control condition, only the placebo group was used as a control group in the BRIMMS protocol for simplicity. Both minor risks and adverse risks were derived from only the intervention group of the clinical trial, which is how risks are commonly provided to patients during standard healthcare.

The following methods were used to present risks and benefits of treatments to MS patients in the BRIMMS protocol, based on earlier findings. All quantitative information was presented using frequencies only (see Experiment 1). The frequencies were presented in the form of N-in-N*X ratio, by keeping the denominator constant and only changing the numerator as necessary to represent the benefits or risks (e.g. 20 out of 1000 get benefits, 50 out of 1000 get risks etc.) (see Experiment 2). All quantitative information was further represented using horizontal bar charts, with numbers added to all charts (see Experiment 1). To provide treatment benefits, absolute terms were used to communicate differences between the intervention group and control group from a hypothetical clinical trial (see Experiment 3). Baseline information was further added to the absolute method of communicating differences between groups (see Experiment 3).

The BRIMMS protocol was provided to patients both aurally (all information was read aloud and only graphs were shown to patients in the written form) and written (all information was given to patients in writing as well as being read aloud) (see appendix 21 for example of the BRIMMS protocol for one hypothetical treatment).

7.2.2.2 Standard consultation

The control group in the present experiment received treatment risks and benefits in a standard consultation style. An approximation to a standard consultation was developed by speaking to MS Nurses at Lewisham and Greenwich NHS Trust and King's

College NHS Trust about how DMD risk and benefit information is presented to patients during consultations. With this information, a preliminary standard consultation was developed and reviewed by another MS nurse. With agreement from the MS nurse, a final standard consultation format was developed.

Only the method of presenting treatment information differed in this consultation compared to the BRIMMS protocol. The minor and adverse risks of treatments were presented using a combination of verbal terms and 1-in-X frequencies, which are recommended for use by EC guidelines (EC Guidelines, 2009). The differences between the intervention and placebo groups of clinical trials were communicated using relative terms, presented in percentages. No graphical formats were provided with the quantitative information.

Similar to the BRIMMS protocol, the standard consultation was presented to patients both aurally (all information was read aloud to patients) and the written form (all information was given to patients in writing as well as being read aloud) (see appendix 22 for example of the standard consultation for one hypothetical treatment).

7.2.2.3 Outcome measures and assessments to measure patient characteristics

The main outcome measures in the current experiment were patients' understanding of the treatment risks (minor and adverse) and benefits, and patients' conflict in their treatment decisions. Patients' feedback on all consultations was also recorded in the experiment. Patient characteristics were also recorded in the present RCT.

Patient understanding

Understanding of treatment risk and benefit information was assessed by asking comprehension questions directly after presenting benefits or risks of medications. Questions for treatment risks were similar to the questions employed in Experiment 1. All

questions for treatment benefits also included the additional questions, as discussed in Experiments 2 and 3 (see section 5.2.2).

In total, patients could score a maximum of 15 points for each treatment, as 15 comprehension questions were provided for each treatment (i.e. 6 questions for treatment benefits after 1 year, 2 years and 5 years, 3 questions each for the two treatment minor risks after 1 year, 2 years and 5 years, and 3 questions for adverse risks of the treatment after 1 years, 2 years and 5 years). The maximum score for each set of treatments was therefore 30 points.

Decisional conflict

Following presentation of one set of treatments (i.e. two hypothetical treatments), patients were required to either choose between the two treatments, choose neither of the treatments or state that they were unsure. Patients' conflict in their decision was measured using the Decisional Conflict Scale (DCS) as described in previous experiments (see section 4.2.2.2).

Patient feedback

In addition to the main outcome measures, patients' feedback for the BRIMMS protocol and standard consultation was recorded by collecting a Likert scale rating (ranging from 0 to 10) on three measures: perceived understanding, perceived satisfaction and perceived preference for each consultation. A score of 0 on the scale meant a negative rating and a score of 10 meant a positive rating.

Patient characteristics

The current experiment also recorded MS patients' characteristics, specifically: patient demographics, numerical reasoning, health literacy, premorbid IQ and symptoms of MS (fatigue, anxiety, depression, verbal memory, visual memory and information-

processing speed). All assessments to record these characteristics have been previously discussed elsewhere (see section 4.2.2.3).

7.2.3 Procedure

The procedure to recruit eligible MS patients for the experiment was the same as those described previously (see section 4.2.3). However, new information sheets and consent forms were provided for this experiment (see appendix 23). Prior to obtaining consent, patients were informed that the experiment was designed to assess which ways of providing treatment information is the most effective at improving understanding of treatment information. Following consent, all patients were tested either at patients' home or clinics. The experiment took approximately 2 hours and 30 minutes to conduct. Each consultation took approximately 20 minutes to administer to patients, but could take up to 30 minutes for some individuals.

Initially, patients were presented with the visual acuity scale to ensure they were eligible to view the remaining experiment. If eligible to continue, patients were asked demographic questions and assessed on the disability status scale at the start of the experiment. Patients were then presented with the hypothetical disease that had four major symptoms (see appendix 20 for hypothetical disease given to patients). The medical disease was read aloud to patients at the beginning of the experiment and was also provided in a written form for patients to refer back to throughout the experiment. Following this, the researcher referred to the sealed envelope to determine the order in which the BRIMMS protocol and the standard consultation would be presented to the patient. The order of the sets and treatments within the set were also specified in the sealed envelope. At the beginning of either the intervention or control conditions, patients were asked to imagine being at the stage of their disease where only two treatments were available for them to take. MS patients were then told that the purpose of the session was for them to make a decision about whether they would choose to take any of the

treatments for the hypothetical disease. Patients did not receive any specific information about the parameters of formats being evaluated, or which condition was the standard consultation and which was a new presentation style. Patients were also blinded to the order in which they received the conditions.

Patients were administered comprehension questions immediately after presentation of each treatment minor risk, adverse risk and benefit. After presentation of both treatments within the RCT condition, patients were asked to make a treatment decision and conflict in their decision was assessed using the DCS. Following administration of the DCS, patients were presented with the three feedback questions. To ensure that no carry-over effects were introduced, patients were given the next RCT condition after a break of 10 minutes. During this break, patients were given tasks to assess patient characteristics, namely: numerical reasoning, health literacy, premorbid IQ, fatigue, mood and cognitive impairments. To ensure that no tasks systematically affected subsequent conditions, the same tasks were presented immediately after each condition (see table 7.1 for the order of tasks presented after each condition). For example, immediately after the BRIMMS protocol aural, patients were given the SDMT task (which assesses information processing speed) and WTAR task (which assesses premorbid IQ), in that order. Therefore, if one task was able to improve understanding of subsequent conditions, the use of a balanced William's square design would mean that all conditions would benefit from such an advantage.

Table 7.1 Order of tasks to assess patient characteristics after each condition

RCT condition	Tasks	Patient characteristics assessed
BRIMMS protocol aural	SDMT	Information processing speed
	WTAR	Premorbid IQ
BRIMMS protocol written	CVLT	Verbal memory
	BVMTR	Visual memory
Standard consultation aural	VESPAR	Numerical reasoning
	REALM-R	Health literacy
Standard consultation written	FSS	Fatigue
	HADS	Anxiety and depression

BVMTR, Brief visuospatial memory test revised; CVLT, California verbal learning test-II recall trials; FSS, Fatigue severity scale, HADS, Hospital anxiety and depression scale; RCT, randomised controlled trial; REALM-R, Rapid estimate of adult literacy in medicine – revised; SDMT; Symbol digit modalities test; VESPAR, Verbal and spatial reasoning task; WTAR, Wechsler test of adult reading

7.2.4 Sample Size

Sample size estimates were based on power calculations for detecting a 0.7 effect size on the DCS outcome measure following the intervention, based on previous RCT studies for interventions designed to improve patients' decisions of treatments (Montgomery, Fahey, & Peters, 2003; Murray et al., 2001; Protheroe, Bower, Chew-Graham, Peters, & Fahey, 2007). It was estimated that for an alpha of 0.05 and power of 0.80 (roughly equivalent to the 'fair' precision level as stated by Senn (2002)), at least 22 MS patients were required in the current experiment. Since patients had to be balanced across all possible sequences of the Williams square (see appendix 19), a sample of 24 MS patients were needed for the present crossover RCT.

7.2.5 Statistical analysis

All statistical analyses were carried out using SPSS 21. Means and standard deviations were provided for all continuous data. Maximum scores were also presented

for all measures in the experiment. Assumptions of parametric analysis were first tested for all outcome measures. A test of normality was conducted for the outcome measure of patients' understanding using the Schapiro-Wilks test. The assumption of normality was significantly violated ($p < .001$) and therefore a nonparametric Friedman two-way analysis of variance was conducted. Where the Friedman test was significant, pairwise comparisons were conducted by using the nonparametric Wilcoxon Signed Ranks test. Bonferroni corrections were applied for multiple comparisons. Effect sizes are calculated for all pairwise comparisons by dividing the z score by the square root of total number of observations, based on Rosenthal's formula (Rosenthal, 1994); where, 0.1, 0.3 and 0.5 equates to small, medium and large effect sizes, respectively.

A second test of normality was conducted for the outcome measure of patients' decisional conflict, as measured by the DCS measure, using the Schapiro-Wilks test. The assumption of normality was not violated ($p > .05$). The assumption of sphericity was tested using the Mauchly's Test of Sphericity and was also not violated ($p > .05$). It was therefore deemed appropriate to conduct a one-way repeated measures ANOVA to analyse the effects of consultations on patients' decisional conflict. Pairwise comparisons were conducted and Bonferroni corrections were applied for multiple comparisons. Standardised DCS scores were used for the purpose of this analysis, as recommended by the authors of the assessment (O'Connor, 1995).

A third test of normality was conducted for the outcome measure of patients' feedback scores using the Shapiro-Wilks test. The assumption of normality was not violated ($p > .05$). The assumption of sphericity was tested using the Mauchly's Test of Sphericity and was violated ($p < .05$). Therefore, a Greenhouse-Geisser correction was applied when interpreting the analysis. A one-way repeated measures ANOVA was conducted. Pairwise comparisons were conducted and Bonferroni correction was applied to correct for multiple comparisons. Patients' feedback scores were obtained by averaging

patient ratings on the measures of perceived understanding, perceived satisfaction and perceived preference.

Bivariate Pearson's product-moment correlations were also computed to assess the relationship between understanding of each of the conditions with raw scores on measures of numerical reasoning, health literacy, premorbid IQ and symptoms of MS. Correlations were conducted with all conditions to assess whether patients' numerical reasoning, health literacy, premorbid IQ and MS symptoms could predict how well patients understood the treatment information across the four different conditions. It was expected that a 'good' condition would increase understanding of treatment information irrespective of numerical reasoning, health literacy, premorbid IQ and MS symptoms, and a 'bad' condition will increase understanding in only some patients. Due to multiple correlations, a stringent alpha of $p < .01$ was applied and accepted as significant.

7.3 Results

7.3.1 Patient demographics

A total of 24 patients were analysed in the RCT, with no dropouts or missing data. Patient demographics is displayed in Table 7.2.

Table 7.2 Patient demographics and disease status for RCT (n=24)

	Mean (SD)	n (%)
Age, years	42.59 (8.63)	
Gender		
Female		21 (87.5)
Male		3 (12.5)
Level of education		
High school		7 (29.2)
College		5 (20.8)
Bachelor's degree		7 (29.2)
Postgraduate		5 (20.8)
Employment status		
Full-time (>16 hours)		11 (45.8)
Part-time (<16 hours)		7 (29.2)
Self-employed		0 (0)
Unemployed		2 (8.3)
Medical leave		4 (16.7)
Retired		0 (0)
Time since MS diagnosis, years	7.88 (4.63)	
HAI disability scale	1.17 (1.34)	
Current DMD		
Interferon betas		8 (33.3)
Glatiramer Acetate		1 (4.2)
Teriflunomide		0 (0)
Fingolimod		7 (29.2)
Alemtuzumab		1 (4.2)
Dimethyl Fumarate		3 (12.5)
Natalizumab		4 (16.7)
Mitoxantrone		0 (0)

DMD= disease-modifying drugs; HAI = Hauser Ambulation Index (65)

* Score of 1 on HAI scale = Able to walk normally but report fatigue interfering with athletic activities

7.3.2 The effect of BRIMMS protocol and standard consultation on patients' understanding

There was a significant effect of consultations (BRIMMS written, BRIMMS aural, standard written, standard aural) on patients' understanding, $X^2(3) = 63.436$, $p < .001$. Pairwise comparisons revealed that understanding was greatest for BRIMMS written, compared to BRIMMS aural ($p < .001$, $r = 0.56$), standard written ($p < .001$, $r = 0.62$) and standard aural ($p < .001$, $r = 0.62$). Understanding was also greater for BRIMMS aural when compared to standard written ($p < .001$, $r = 0.62$) and standard aural ($p < .001$, $r = 0.62$). There was no difference between understanding for standard consultation aural and standard consultation written ($p = 0.985$). Mean scores for patients' understanding on all conditions are presented below (see table 7.3). Higher mean scores indicate greater understanding of treatment information.

Table 7.3 Mean scores for patient understanding across all conditions

Conditions	Max score	Mean (SD)	Confidence interval (95%)
BRIMMS protocol written	30	27.79 (2.41)	26.77 – 28.81
BRIMMS protocol aural	30	24.88 (2.94)	23.63 – 26.12
Standard consultation written	30	3.71 (2.29)	2.74 – 4.68
Standard consultation aural	30	3.71 (2.96)	2.46 – 4.96

BRIMMS, Benefit and risk information for medication in Multiple Sclerosis

7.3.3 The effect of BRIMMS protocol and standard consultation on decisional conflict

There was a significant effect of conditions (BRIMMS aural, BRIMMS written, standard aural, standard written) on patients' decisional conflict, $F(3,69) = 75.109$, $p < 0.001$, partial $\eta^2 = .87$. Pairwise comparisons revealed that conflict in decisions were reduced the most for the BRIMMS written protocol, compared to standard written ($p < .001$) and standard aural ($p < .001$). Decisional conflict was also reduced the most for

BRIMMS aural compared to standard written ($p<.001$) and standard aural ($p<.001$). There was no difference in decisional conflict for standard written compared to standard aural ($p=.216$). There was no difference between decisional conflict for patients presented either the BRIMMS written or BRIMMS aural protocol ($p=1.00$). Mean scores for patients' decisional conflict for all conditions are presented below (see table 7.4). Lower mean scores indicate reduced decisional conflict.

Table 7.4 Mean scores for decisional conflict across all conditions

Conditions	Max score	Mean (SD)	Confidence interval (95%)
BRIMMS protocol written	100	26.17 (8.06)	22.77 – 29.58
BRIMMS protocol aural	100	25.78 (7.98)	22.41 – 29.15
Standard consultation written	100	47.61 (11.97)	42.60 – 52.71
Standard consultation aural	100	52.80 (10.43)	48.40 – 57.20

BRIMMS, Benefit and risk information for medication in Multiple Sclerosis; DCS, Decisional conflict scale

7.3.4 Patients' feedback on BRIMMS protocol and standard consultation

A one-way repeated measures ANOVA found a significant main effect of condition on patients' feedback scores, $F(1.27, 29.24) = 111.835$, $p<0.001$. Pairwise comparisons revealed that BRIMMS written was rated more positively by patients compared to BRIMMS aural ($p<.001$), standard written ($p<.001$) and standard aural ($p<.001$). More positive ratings were also given for BRIMMS aural when compared to standard written ($p<.001$) and standard aural ($p<.001$). There was no difference between patients' feedback for standard written and standard aural ($p<.01$). Mean scores for patient feedback on all conditions are presented below (see table 7.5).

Table 7.5 Mean scores for patient feedback across all conditions

Conditions	Max score	Mean (SD)	Confidence interval (95%)
BRIMMS protocol written	10	8.63 (.89)	8.25 – 9.00
BRIMMS protocol aural	10	7.92 (.97)	7.51 – 8.33
Standard consultation written	10	3.78 (2.06)	2.91 – 4.65
Standard consultation aural	10	3.26 (1.91)	2.46 – 4.07

BRIMMS, Benefit and risk information for medication in Multiple Sclerosis

7.3.5 Patient understanding and patient characteristics

Patients were assessed for numerical reasoning skills, health literacy, premorbid IQ and MS symptoms in the current experiment. As shown in table 7.6, MS patients in the current experiment mostly showed symptoms of anxiety, fatigue and cognitive impairments. Mean scores for all measures assessing patient characteristics are presented in table 7.7. Mean scores show that patients on average had high literacy and scored high on fatigue, whereas other patient characteristics showed greater variability between patients.

Table 7.6 Patients impaired on assessments of numerical reasoning, health literacy, premorbid IQ and MS symptoms (n=24)

Patient characteristics and MS symptoms	n (%)
Health literacy	2 (8.3)
Numerical reasoning	1 (4.2)
Depression	4 (16.7)
Anxiety	5 (33.3)
Fatigue	13 (54.2)
Premorbid IQ	1 (4.2)
Information processing speed	0 (0)
Verbal memory	7 (29.2)
Visual memory	10 (41.7)

Table 7.7 Maximum and mean scores for assessments measuring patient characteristics

Patient characteristics and MS symptoms	Max score	Mean	SD
Numerical reasoning	25	16.63	3.00
Literacy	8	7.79	.59
Anxiety	21	6.88	4.20
Depression	21	5.38	4.45
Fatigue	63	44.71	12.84
Premorbid IQ	50	35.83	8.02
Information processing speed	110	63.79	6.72
Verbal memory	80	49.58	9.82
Visual memory	36	22.04	6.08

Bivariate product Pearson correlations were computed for all conditions to assess whether patients' numerical reasoning, health literacy, premorbid IQ and MS symptoms could predict how well patients understood the treatment information across the four different conditions. It was expected that the BRIMMS protocol written and aural (the conditions with the best understanding) would increase understanding of treatment information irrespective of numerical reasoning, health literacy, premorbid IQ and MS symptoms.

Only two patient characteristics were correlated with understanding scores in BRIMMS protocol written: health literacy ($r=.519$, $p<.01$) and depression ($r=-.539$, $p<.01$) (see table 7.8). Three patient characteristics were correlated with understanding scores in the BRIMMS protocol aural: anxiety ($r=.596$, $p<.01$), depression ($r=.674$, $p<.01$) and verbal memory ($r=.549$, $p<.01$). In addition, correlation for treatment understanding score on standard consultation written and patient characteristics revealed significant correlations for numerical reasoning ($r=.564$, $p<.01$), premorbid IQ ($r=.543$, $p<.01$), information processing-speed ($r=.558$, $p<.01$) and verbal memory ($r=.585$, $p<.01$). Similarly, correlations for treatment understanding score on standard consultation aural

revealed significant correlations for numerical reasoning ($r=.550$, $p<.01$), premorbid IQ ($r=.504$, $p<.01$), information processing-speed ($r=.590$, $p<.01$) and verbal memory ($r=.647$, $p<.01$).

Table 7.8 Correlations between patient understanding and patient characteristics across all conditions

Assessment scores	Understanding scores			
	BRIMMS written	BRIMMS aural	Standard written	Standard aural
Numerical reasoning	.391	.359	.564**	.550**
Health literacy	.519**	.362	.469*	.414*
Anxiety	-.328	-.596**	-.450*	-.300
Depression	-.539**	-.674**	-.453*	-.299
Fatigue	-.117	-.493*	-.338	.007
Premorbid IQ	.385	.422*	.543**	.504**
Info processing speed	.335	.432*	.558**	.590**
Verbal memory	.302	.549**	.585**	.647**
Visual memory	.116	.363	.216	.378

* = indicates significance at $p<.05$ level; ** at $p<.01$ level; correlations in bold accepted as significant due to multiple correlations; BRIMMS, Benefit and risk information for medication in Multiple Sclerosis; Info, information

7.4 Discussion

Patients should accurately understand the risks and benefits of treatments in order to make informed treatment decisions in a shared decision-making context (Colligan, Metzler, & Tiriyaki, 2016; Godolphin, 2009). However, MS patients do not satisfactorily understand the risks and benefits of DMDs presented during standard healthcare (Reen et al., 2017). Previous experiments in this thesis have shown that MS patients' understanding can be affected by methods used to present treatment information (see chapters 4-6). A BRIMMS protocol was designed in the current experiment to combine the best methods of presenting medication risk and benefit information based on findings

from Experiments 1 to 3. This protocol was developed in both a written form and as an aural presentation. The efficacy of this protocol on patients' understanding and conflict in their treatment decisions was evaluated using a crossover RCT by comparing this to standard methods of providing treatment information during consultations. All requirements for an effective crossover design were met: testing was conducted in patients with a chronic disease, and carryover effects were minimised by providing a 10-minute break before each condition, as well as employing completely different treatments with different levels of risks and benefits for each condition presented to the same patient.

As predicted, the BRIMMS protocol presented either in written form or presented aurally greatly improved MS patients' understanding of treatment risks and benefits compared to treatment information provided during standard consultations. These results further support the evidence that patients show poor understanding when treatment information is presented during standard healthcare (Reen et al., 2017), and that effective presentation methods, as directly tested with MS patients, have the potential to improve the way MS patients understand the risks and benefits of DMDs (see chapters 4-6 and figure 6.2). Interestingly, the written BRIMMS protocol was considerably better at improving MS patients' understanding of treatment information than the BRIMMS protocol presented aurally. One reason for this effect may be because the BRIMMS protocol was designed based on the best written presentation methods from previous experiments, which may not have been the best aural presentation methods for providing treatment information. Therefore, additional studies should be conducted with MS patients to assess the best aural presentation methods for providing treatment information.

Nevertheless, both BRIMMS protocols greatly improved MS patients' understanding of treatment information, which can have several benefits for MS patients. Implementing the BRIMMS protocol in consultations could improve shared decision-making by ensuring that patients only choose treatments with the level of risks and

benefits that patients would prefer. This is important considering that MS patients' preferences play a large role in their decision to choose a treatment (Reen et al., 2017). Treatment decisions based on patient preferences can also likely improve adherence to treatment, as patients will have realistic expectations for the risks and benefits of treatments. Increased adherence to DMDs can lead to better clinical outcomes for MS patients, especially since DMDs need to be adhered to for long periods of time to effectively delay the progression of disease (Halpern et al., 2011; Steinberg et al., 2010; Tan et al., 2011; Winkelmann et al., 2016).

In addition to patient understanding, the BRIMMS protocol in both written and aural form showed significant reductions in patients' conflict in the treatment decisions made in this experiment, in comparison to treatment information presented using standard method of consultations. This is consistent with interventions that have been designed to improve decision-making for non-MS clinical patients (Montgomery et al., 2003; Murray et al., 2001; Protheroe et al., 2007). Therefore, the current results suggest that patients presented with the BRIMMS protocol were able to make treatment decisions based on personal preferences of treatment risks and benefits, and were thus more confident in their decisions. Although it is reasonable to expect that an intervention that could improve patients' understanding about treatment options would also reduce conflict in their choice for one of those options, it should be noted that Experiments 1 to 3 found no correlations between patients' understanding of treatment information and reduction in decisional conflict (see chapters 4 to 6). This indicates that the BRIMMS protocol may have reduced decisional conflict due to some additional reasons which were not necessarily related with improvements in understanding. Given that the BRIMMS protocol is a complex intervention, it was not possible to isolate the specific components to determine which aspect of the protocol could have reduced patients' decisional conflict.

Patients' feedback for all conditions was also recorded in the present RCT. Patients significantly favoured the BRIMMS protocol in both written and aural forms compared to information provided in standard consultations; patients reported that they better understood the treatment information, were better satisfied with the presentation of information and strongly preferred the BRIMMS protocol in comparison to standard consultations. In addition, patients rated the written form of the BRIMMS protocol more favourably than the BRIMS in aural form.

Patients' understanding scores on all conditions were also correlated with patient characteristics in this experiment. It was expected that a good intervention would be able to improve patients' understanding irrespective of factors such as poor numerical reasoning, poor health literacy or impairments in information processing speed, verbal memory and visual memory. This was mostly found to be the case for the written BRIMMS protocol which showed the greatest improvements in understanding; understanding was improved irrespective of patients' numerical reasoning skills, levels of anxiety and fatigue, premorbid IQ, information processing speed, verbal memory skills and visual memory skills. Only health literacy and depression predicted understanding of the BRIMMS written protocol. Whereas, patients who experienced high anxiety, were more depressed or had poor verbal memory, had poorer understanding on the BRIMMS aural protocol. For those given the standard consultations, patients with poor numerical reasoning, low premorbid IQ, impaired information processing speed or poor verbal memory were predicted to have poor understanding. Thus, the BRIMMS written protocol helped improve understanding despite the presence of these patient characteristics which predicted (and probably affected) understanding in other conditions. However, there is still room for improvement. The BRIMMS written protocol should be adapted so that understanding improves even when patients have poor health literacy and are highly depressed.

Previous interventions designed to improve MS patients' understanding of treatment risks and benefits have shown moderate success; interventions show improvements in accuracy of treatment risks but overestimation of DMD benefits persists following interventions (Reen et al., 2017a). Several interventions also present treatment information using methods that have not been previously tested for efficacy with MS patients. Moreover, many interventions are designed to be implemented beyond consultations (Reen et al., 2017a) despite consultations with health professionals being the most common source of receiving information about treatments (see MS patients survey in Chapter 3). Additionally, only one intervention with MS patients has examined whether understanding could be improved for patients with symptoms that could likely confound patient understanding of treatment information (Basso et al., 2010). The current intervention thus addresses all these issues: BRIMMS written and aural protocol shows improvements in understanding of treatment risks and benefits combined, can be implemented in consultations by health professionals and shows improvements in understanding regardless of several patient characteristics that may confound understanding of treatment information.

Despite the benefit of the BRIMMS protocol, the findings should be interpreted with caution due to a number of limitations. First, the experimenter was not blinded in the current RCT. This could have indirectly affected how the BRIMMS protocol and standard consultations were presented to MS patients during the experiment or how the comprehension questions were scored. Secondly, treatment information across all conditions were provided by a non-clinical experimenter. Patients may interact differently when treatment information is presented by health professionals in real consultations. Health professionals are also likely to adapt the treatment information to patients' needs when providing treatment information during real consultations, or engage in questions and answers with patients during consultations. However, interventions that have been

designed with an interactive component for MS patients do not seem to affect understanding differently to more passive interventions (Reen et al., 2017a). Third, although best efforts were made to ensure that the standard consultation in the current experiment reflected consultations provided to MS patients within the UK, it is likely that current consultations in the UK vary between each session with patients and between health professionals. In addition, patients in the current experiment were required to answer comprehension questions directly after presentation of treatment risks or benefits which is not common practise during standard consultations. In fact, performance on these questions could have been affected by poor memory rather than poor understanding. To minimise the effects of forgetting however, patients in this experiment were given comprehension questions immediately after presentation of one treatment outcome. Finally, patients had no prior knowledge about the hypothetical treatments presented in the current RCT. Yet, many MS patients report searching for treatment information prior to discussing this with health professionals during consultations (see MS patient surveys in chapter 3). This may positively or negatively affect patients' understanding of treatment information during real consultations.

It is also important to acknowledge the applicability of the BRIMMS intervention for administration during real consultations with patients. The BRIMMS intervention in the current study took approximately 20 minutes to administer, but could take up to 30 minutes for some individuals. However, time availability for patients during real consultations is dictated by the pre-defined slots available for patients and other external factors that may occur during clinic visits (e.g. previous consultations that have overrun, availability of staff), which could impact the time available during a consultation to administer the BRIMMS intervention to patients. In addition, patients are likely to talk about specific information needs, personal preferences associated with treatments and emotions about the decision-making process during a real consultation, which can further

influence the duration of consultations with health professionals. Moreover, patients are likely to have multiple consultations during the decision-making process, often making decisions alongside families and carers. All these factors need to be taken into account when considering the application of the BRIMMS intervention during consultations in real clinics.

There are a number of ways that the applicability of the BRIMMS protocol in real clinics could be improved. First, the length of the BRIMMS protocol in the current study was similar to that of the standard consultation in the current experiment, indicating that it is possible to replace the formats used in standard consultations with the formats in BRIMMS without substantially increasing the length of consultations. Second, it may be possible to set up a dedicated consultation to provide treatment information using the BRIMMS protocol, prior to typical consultations with health professionals. Patients' needs and preferences can then be discussed during regular consultations. Third, the BRIMMS protocol should be evaluated in the future with carers and families of patients who are likely to be involved in treatment decision-making process during consultations. Finally, the BRIMMS protocol should be developed and evaluated for different administration methods to complement the BRIMMS protocol in consultations, such as by basing patient leaflets and patient websites on this protocol."

7.4.1 Conclusion

Combining the best presentation methods from previously conducted experiments into a BRIMMS protocol greatly improved patients' understanding of treatment risks and benefits, and reduced conflict in their decision to take the treatment compared to treatment information presented using standard consultations. These improvements were generally greater when the BRIMMS protocol was presented in a written form compared to BRIMMS presented aurally. Patients also positively rated the BRIMMS protocol compared to standard consultation methods. From these findings, it is recommended that

following further evaluation, the BRIMMS protocol should be implemented in real consultations between health professionals and MS patients when making decisions about DMDs.

Chapter 8: General discussion

MS is a chronic disease that affects over 2.3 million people around the world (Browne et al., 2014). Patients diagnosed with MS can present with a multitude of symptoms that can vary between individuals, including: physical symptoms, fatigue, affective disorders and cognitive impairments (Compston & Coles, 2008). As the disease continues to progress, the symptoms of MS can increase in severity, leading to disability in many patients. Although there is no cure for MS at present, extensive research in the last two decades have increased treatment options that can delay the progression of disease in the form of disease-modifying drugs (DMDs). All DMDs have different levels of risks and benefits, with the effects of treatments varying between patients (English & Aloï, 2015; Wingerchuk & Weinshenker, 2016; Winkelmann et al., 2016).

Decisions about the most suitable DMD for MS patients should ideally be made within a shared decision-making context, commonly employed as part of a patient-centred approach to healthcare (Barry & Edgman-Levitan, 2012; Charles et al., 1997, 1999; Godolphin, 2009). A prerequisite of shared decision-making is that patients be fully informed about the risks and benefits of all eligible treatments, and that these are communicated by health professionals in a manner which is easy to understand (Barry & Edgman-Levitan, 2012; Charles et al., 1997). A number of recommendations have been made to ensure clear and comprehensible information is provided to patients making decisions about treatments (Bunge et al., 2010; Edwards et al., 2002; Fagerlin et al., 2011; Paling, 2003). These recommendations are generally based on findings from studies conducted with non-clinical populations and patients from numerous clinical diseases. However, in order to determine how understanding of the complex risk and benefit profiles of DMDs can be improved, it is important that the best methods of providing

treatment information are empirically tested with the population group most likely to utilise the treatment information during decision-making.

8.1. Thesis summary

The present thesis proposed to develop an integrated intervention to provide information about DMD risks and benefits to MS patients; the Benefit and Risk Information for Medications in Multiple Sclerosis (BRIMMS) protocol. In order to develop the BRIMMS protocol, it was first necessary to establish the current status of MS patients' understanding of DMD risks and benefits, and the need to improve MS patients' understanding within routine healthcare. Following this, reviews of existing methods of presenting treatment information to non-clinical and clinical populations informed the design of a theoretical framework about presentation methods that could improve understanding of MS patients. With this theoretical framework in mind, the different presentation methods were empirically tested with MS patients to determine the best methods that could improve understanding of treatment risks and benefits. Findings from these experiments were used to adapt the theoretical framework. The best presentation methods were then combined in the form of the BRIMMS protocol, which was subsequently compared with standard methods of receiving treatment information in current healthcare. The experiments employed in this thesis were therefore the first to provide recommendations for evidence-based practise based on a comprehensive assessment of methods to present treatment information.

8.1.1 Chapter 2: Systematic reviews

At the first stage of the thesis, a systematic review of the literature was conducted to explore MS patients' current understanding and preferences for risks and benefits of DMDs (Reen et al., 2017). This review found that MS patients' do not satisfactorily understand DMD information they receive within standard healthcare. This review also showed that MS patients have individual preferences for the risks and benefits of

treatments they are willing to take, which could affect the decision to initiate a DMD. Given that patients in this review generally showed a trend towards underestimating the risks of DMDs and overestimation of DMD benefits, it is likely that MS patients choose to initiate treatments with risk-benefit profiles that do not correspond with their preferred levels of risks and benefits. This can lead to reduced treatment adherence which can have a number of clinical consequences for MS patients (Halpern et al., 2011; Steinberg et al., 2010; Tan et al., 2011).

A second systematic review was conducted to evaluate the interventions that have been designed to improve understanding of treatment risks and benefits for MS patients beyond standard healthcare (Reen et al., 2017a). The review found that, in general, understanding of DMD risks were improved following intervention but overestimation of DMDs persisted. However, the design and implementation of these interventions varied considerably between studies in this review. Interventions that were more comprehensive and interactive performed similarly to simple interventions. The methods of providing treatment risk and benefit information during the interventions had not always been empirically tested with MS patients. In addition, patient characteristics that could confound understanding of treatment information, such as cognitive impairments in MS, were not considered by the majority of studies in this review.

Together, both these reviews identify a need for an intervention that could optimise MS patients' understanding of DMD risks and benefits using presentation methods that are empirically tested with MS patients.

8.1.2 Chapter 3: MS patient and MS nurse surveys

The current chapter sought to explore MS patients' experiences of receiving treatment information within standard healthcare in the UK. MS nurses were also assessed about their experiences regarding how well MS patients understand current DMD information and how this could be improved. A survey methodology was

employed. Since the surveys were expected to inform the need for subsequent experiments with MS patients, an exploratory analysis of surveys was deemed sufficient. The results from these surveys supported findings from the systematic review in chapter 2. Approximately half of the MS patients reported poor understanding of DMD risks and benefits which was supported by feedback from MS nurses. MS patients and nurses also reported that patients commonly receive treatment information during consultations with health professionals, followed by online websites. In addition, both patients and nurses reported that current healthcare services could be improved by providing clear information about DMD risks and benefits so that patients could effectively compare treatments to make treatment decisions.

In conjunction with the findings from the systematic review, the survey results identified a need to improve MS patients' understanding of treatment risks and benefits primarily provided by health professionals during consultations. For this reason, experiments were conducted with MS patients in subsequent chapters to assess the best methods to present treatment information that could optimise understanding.

8.1.3 Chapter 4: Experiment 1

EC guidelines have recommended the use of verbal formats when presenting information about treatment risks and benefits to patients (EC Guidelines, 1998, 2009), which are employed in current clinical practise for providing DMD information to MS patients (see appendix 11). However, studies indicate that treatment information is often misunderstood when provided using verbal formats (Berry et al., 2003; Berry et al., 2002; Knapp et al., 2009; Knapp et al., 2004; Knapp et al., 2015). Numerical formats have also been recommended for presentation of the risks and benefits of treatments (Bunge et al., 2010; Lipkus, 2007; Paling, 2003) and are used in current clinical practise for MS patients (see appendix 11). However, studies have not conclusively established whether presenting numbers in the form of frequencies or percentages can better improve

understanding of treatment information (Bramwell et al., 2006; Cuite et al., 2008; Gurmankin et al., 2004; Peters et al., 2011; Waters et al., 2006; Woolshin & Schwartz, 2011). Moreover, the use of graphical formats have also been encouraged in order to facilitate understanding of treatment information (Garcia-Retamero & Galesic, 2010b; Garcia-Retamero & Hoffrage, 2013; Lipkus, 2007; Tait et al., 2010). Studies that have reviewed the effects of graphical formats such as bar charts, line graphs, pictographs and pie charts on understanding of treatment information, generally show that pictographs and bar charts are more favourable at improving understanding than other graphical formats (Brewer et al., 2012; Hamstra et al., 2014; Hawley et al., 2008; McCaffery et al., 2012; Schapira et al., 2006; Tait et al., 2012, 2010; Zikmund-Fisher, Fagerlin, Roberts, Derry, & Ubel, 2008). However, studies assessing verbal, numerical and graphical formats on understanding have generally only been conducted with non-clinical populations or with clinical populations other than MS. The effects of these formats on MS patients' understanding had not been explored.

Experiment 1 was therefore the first experiment to conduct a comprehensive assessment of how different verbal, numerical and graphical formats could facilitate MS patients' understanding of hypothetical treatment risks and benefits. Patients showed poor understanding of treatment risks and benefits when presented in verbal formats, but greater understanding when information was presented numerically. Specifically, frequencies were understood better than percentages. In terms of graphical formats, bar charts and line graphs showed better understanding of treatment information in comparison to pictographs and pie charts. In particular, bar charts were better understood when presented horizontally rather than vertically. Similarly, pictographs were better understood when the figures showing people affected by the risks or benefiting from the treatment were consecutively arranged rather than presented randomly. Pie charts were the least understood graphical format. However, when numbers were presented alongside

graphical formats, all formats were well understood by MS patients. Patients' understanding across all methods was not reliably related with patients' conflict in their treatment decisions. However, patients with low numerical reasoning skills, low health literacy, poor premorbid IQ, slower information processing or poor verbal memory skills showed poor understanding across all formats.

8.1.4 Chapter 5: Experiment 2

Although Experiment 1 showed that frequencies could improve MS patients' understanding of treatment information, the ratios used to present these frequencies to MS patients were not assessed. Frequencies can either be presented in the ratio 1-in-X, where the numerator is always kept constant at 1 (e.g. 1 in 20, 1 in 5), or can be presented using the N-in-N*X ratio where the denominator is always kept constant (e.g. 50 in 1000, 200 in 1000). Both types of frequencies are employed within current clinical practise to provide DMD information to MS patients (see appendix 11). Experimental studies generally show that people are poor at understanding treatment information when frequencies were presented with the 1-in-X ratio compared to the N-in-N*X ratio (Cuite et al., 2008; Grimes & Snively, 1999; Pighin et al., 2011, 2013, 2015; Sirota et al., 2014; Witteman, Zikmund-Fisher, Waters, Gavaruzzi, & Fagerlin, 2011). However, this effect has not been previously observed with MS patients. The manner in which treatment risks and benefits are framed (i.e. positively or negatively) has also been shown to affect decisions (McNeil et al., 1982; Meyerowitz & Chaiken, 1987; Peters et al., 2011; Rothman et al., 2006; Tversky & Kahneman, 1981; Zimmermann et al., 2000). Only two studies assessed understanding of treatment information presented in different frames and found that risks and benefits framed positively were better understood (Armstrong et al., 2002; Carling et al., 2010). Yet, both these studies were conducted with non-clinical populations only.

Experiment 2 therefore sought to determine how different frequency ratios and different ways of framing treatment information could affect how risks and benefits were understood by MS patients. Consistent with previous findings, the 1-in-X frequency ratio was the least understood format. In regards to framing, negatively framed treatment risks and benefits were better understood by MS patients. However, the size of this effect was very small. Similar to Experiment 1, patients' understanding across all methods was not reliably related with patients' conflict in their treatment decisions. However, patients with low numerical reasoning skills, poor premorbid IQ, slow information processing speed or poor verbal memory skills showed poor understanding of ratios and framing of information.

8.1.5 Chapter 6: Experiment 3

The risk-benefit profiles of DMDs can be established from clinical trials by comparing the risks and benefits of patients taking the treatment of interest to the risks and benefits of patients taking a placebo or an existing treatment (Braune et al., 2015; Fogarty et al., 2016; Miller et al., 2014). It is important that patients are able to understand the differences between these groups in order to make informed treatment decisions. There are a number of ways to communicate these differences and include: absolute terms, relative terms and numbers needed to treat or harm. Relative terms are commonly employed in current clinical practise with MS patients (see appendix 11). Previous studies have varied considerably in their assessment of understanding of differences communicated in different methods. Nevertheless, there was a trend showing that differences communicated using absolute terms could improve understanding of treatment risks and benefits compared to other methods (Bodemer et al., 2014; Covey, 2011; Hembroff et al., 2004; Kristiansen et al., 2002; O'Donoghue et al., 2014; Perneger & Agoritsas, 2011; Sheridan et al., 2003). Only one study was conducted with MS

patients, but only evaluated one method of communicating differences from groups in a clinical trial (Kasper et al., 2006).

Experiment 3 was therefore the first experiment to evaluate the effects of understanding treatment risks and benefits when differences were communicated in either absolute terms, relative terms or numbers needed to treat to MS patients. Patients showed greater understanding of treatment information when presented using absolute terms compared to all other methods. However, when baseline information (i.e. comprehensive information about the number of people in each group) was added, patients showed greater understanding of treatments when presented in all methods. Similar to previous experiments, patients' understanding across all methods was not reliably related with patients' conflict in their treatment decisions. However, patients with low numerical reasoning skills, poor premorbid IQ, slow information processing or poor verbal memory skills showed poor understanding of treatments when clinical trial groups were communicated in all methods.

8.1.6 Chapter 7: Experiment 4

The main goal of this thesis was to develop the BRIMMS protocol by integrating the best methods of presenting treatment information to MS patients from Experiments 1 to 3. The following methods were used: frequencies presented in the form of N-in-N*X ratio, horizontal bar charts with numbers presented alongside each bar and all differences communicated using absolute terms. All risks were framed negatively and benefits framed positively, due to the small effects of framing on understanding of treatment information in Experiment 2 and in accordance with guidelines about the best manners to present treatment information within interventions (Bunge et al., 2010). The BRIMMS protocol was compared using a randomised controlled trial with a crossover design, with standard methods of providing treatment information to MS patients in consultations. Both the BRIMMS protocol and the standard consultation was provided in a written and

aural form. Patients were also assessed on their decisional conflict following their treatment choice after each condition and were also asked to provide feedback on all conditions. Understanding scores for all conditions were further correlated with patient characteristics.

Experiment 4 found that the BRIMMS protocol greatly increased MS patients' understanding of treatment information compared to standard consultations. Specifically, the BRIMMS written protocol was the most effective. In fact, understanding scores for the BRIMMS protocol were not related to several patient characteristics, indicating that patients showed improvements irrespective of numerical reasoning skills, premorbid IQ and cognitive impairments. However, patients with high levels of depression and poor health literacy still showed poor understanding when presented with the BRIMMS protocol. Additionally, both BRIMMS protocols reduced conflict in treatment decisions compared to standard consultation. Patients also rated the BRIMMS written and BRIMMS aural protocols positively compared to standard consultations. Overall, the BRIMMS protocol was found to be an effective intervention to present MS patients with treatment information.

8.2. Limitations and future research

In addition to the specific limitations discussed in each chapter, there are a number of overarching limitations of the whole thesis which should be taken into account. Future work based on the findings from this thesis will also be discussed.

All experiments with MS patients were conducted using hypothetical treatment risk and benefit information. Although the levels of risks and benefits provided to patients were based on real DMD risk and benefit profiles, patients' understanding of the hypothetical treatments may not apply to real DMD risks and benefits. In particular, specific risks and benefits of DMDs may be more salient for individual MS patients which could affect how these risks and benefits are understood in real clinical situations.

This may mean that the BRIMMS protocol, based on presentation methods from hypothetical treatment information, may not exactly mimic understanding of real DMD information. However, the choice to employ hypothetical treatments in the thesis was made due to several reasons. First, since the research was conducted by a non-clinical researcher, providing real treatment information to patients without support from health professionals was not deemed suitable. Second, the majority of studies that have been conducted with clinical populations about the effects of different presentation methods have employed hypothetical clinical scenarios (e.g., Chapman, Litton, Chamberlain, & Ho, 2015; O'Donoghue et al., 2014; Perneger & Agoritsas, 2011; Sheridan et al., 2003). However, with these limitations in mind, it is important that the BRIMMS protocol be validated for use with real DMD information before this can be implemented in real clinical situations.

Another limitation resulting from employing hypothetical treatment information in the current thesis is that patients had no prior knowledge of the risk and benefit profiles of treatments when comprehending the information. This may be different to real treatment information in real clinical situations, since many patients report conducting independent research about treatments prior to receiving treatment information from health professionals (Colombo et al., 2014; Marrie, Salter, Tyry, Fox, & Cutter, 2013; Synnot et al., 2014; also see chapter 3). Having no prior knowledge of the risks and benefits of treatments in the present thesis could have increased the cognitive load for patients and consequently affected understanding. Despite this, patients consistently showed greater understanding of certain presentation methods which indicates that these methods were effective even with a higher cognitive load. To note, external information that patients search could also be inaccurate or outdated which could negatively impact understanding and lead to cognitive dissonance during treatment decisions. For this reason, the presentation methods that have been employed in the present thesis should be

evaluated in real clinical scenarios to ensure that understanding can improve irrespective of inaccurate information elsewhere.

Patients' conflict in their treatment decisions was assessed for a rapid decision about whether to initiate a hypothetical treatment across all experiments in this thesis. However, real treatment decisions may often be adopted after a long deliberation process and following discussions with relatives, other health professionals and other patients (see Chapter 3). This may be a reason why no relationship was observed between treatment understanding scores and decisional conflict in Experiments 1 to 3. Yet, patients did show differences in decisional conflict scores following the BRIMMS protocol and standard consultations, implying that decisional conflict could be affected even after prompt treatment decisions. Nevertheless, patients' conflict in their treatment decisions following the BRIMMS protocol should be measured after patients have had time to carefully consider the treatments they would be willing to initiate in a real clinical situation.

Patients' preferences for treatment risks and benefits can greatly influence their choice of treatment (Currie et al., 2014; Fraenkel, 2013; Gong et al., 2015) and is another important aspect of shared decision-making (Charles et al., 1997, 1999). The systematic review conducted in this thesis also showed that MS patients' preferences could influence their choice to initiate treatments with specific risk-benefit profiles (Reen et al., 2017). However, patients' preferences were not measured in experiments within this thesis. Future work should therefore consider whether the treatment choice made following different presentation methods was related with patient preferences to determine whether an effective decision had been made. Additional outcome measures, such as adherence to treatment, satisfaction with treatment and patient autonomy could also be employed in future studies to assess whether effective treatment decisions had been made following different presentation methods or the BRIMMS protocol.

The effect of specific patient characteristics on patients' understanding scores across all experiments should be interpreted with caution. All experiments in the present thesis were powered to detect differences in the validated DCS measure (see sections 4.2.4, 5.2.4 and 6.2.4). Thus, factors such as fatigue, anxiety and depression may not have shown high correlations with patient understanding scores due to low effect sizes. However, the fact that patients' numerical reasoning skills, level of premorbid IQ and cognitive impairments did show reliable correlations with understanding scores across all experiments suggests that these correlations have a larger effect. Patients with MS can also experience language impairments during their disease (Renauld, Mohamed-Saïd, & Macoir, 2017) which may have affected patients' understanding of treatment information in the current thesis. However, language impairments were not assessed as this symptom is still poorly defined in MS and no suitable assessment measure to detect language impairments in MS patients has been identified (Renauld et al., 2017).

Moreover, there was a selection bias associated with MS patients who were recruited in experiments 1 to 4 of the thesis. Patients that consented to take part were from an urban metropolitan society and results from this sample may not necessarily relate with patients from rural backgrounds in the UK. However, the variability in levels of numerical reasoning and premorbid IQ between patients indicates that there was a lot of diversity in the patient population (see table 8.2). Furthermore, patients were generally representative of the MS population in the UK (Ford et al., 2012), as the sample consisted of majority females with an average age of approximately 45 years (see table 8.1). Patients across Experiments 1 to 4 also experienced MS symptoms typical of a MS population (see section 1.1.2 for overview of MS symptoms). Patients were more commonly impaired on fatigue across all experiments, followed by cognitive impairments and depression (see table 8.3). Patients across Experiments 1 to 4 were also taking a range of first-line and later-line DMDs further increasing the representativeness of the current

sample (see section 1.2 for DMD review). The majority of patients across all experiments were taking interferons, followed by fingolimod and natalizumab (see table 8.1). Despite being a representative MS sample overall, it should be noted that the patients given the BRIMMS protocol (Experiment 4) showed some differences to the patients that were recruited in Experiments 1 to 3. For instance, MS patients in Experiment 4 did not show any impairments on information processing speed and had been diagnosed with MS for a shorter period of time. However, all other patient characteristics, DMDs taken and symptoms of MS for patients in Experiment 4 were similar to the previous experiments (see tables 8.1, 8.2 and 8.3).

The attitudes of MS patients that consented to take part in all experiments of this thesis may also have differed to patients not involved in the research. For example, patients in the present sample may have been more autonomous and likely to be involved in treatment decision-making given their interest in a research study about understanding of treatment information. Patient autonomy was not tested in the present thesis and should be assessed in future experiments. Nevertheless, highly autonomous patients are more likely to make decisions based on treatment risk and benefit information rather than by passive recommendations made by health professionals, and it is therefore necessary to include autonomous patients in research about informed treatment decisions.

Table 8.1 Comparison of patient demographics in Experiments 1, 2, 3 and 4

Patient demographics	Exp 1 (n=45)	Exp 2 and 3 (n=45)	Exp 4 (n=24)
Age in years, mean (SD)	42.51 (9.46)	46.76 (10.50)	42.59 (8.63)
Gender, n (%)			
Female	34 (75.6)	36 (80.0)	21 (87.5)
Male	11 (24.4)	9 (20.0)	3 (12.5)
Level of education, n (%)			
High school	13 (28.9)	15 (33.3)	7 (29.2)
College	7 (15.6)	11 (24.4)	5 (20.8)
Bachelor's degree	15 (33.3)	8 (17.8)	7 (29.2)
Postgraduate	10 (22.2)	11 (24.4)	5 (20.8)
Employment status, n (%)			
Full-time (>16 hours)	17 (37.8)	13 (28.9)	11 (45.8)
Part-time (<16 hours)	8 (17.8)	10 (22.2)	7 (29.2)
Self-employed	6 (13.3)	7 (15.6)	0 (0)
Unemployed	9 (20.0)	11 (24.4)	2 (8.3)
Medical leave	5 (11.1)	3 (6.7)	4 (16.7)
Retired	0 (0)	1 (2.2)	0 (0)
Time since MS diagnosis in years, mean (SD)	9.80 (8.10)	10.89 (8.51)	7.88 (4.63)
HAI disability scale, mean (SD)	1.49 (1.67)	1.64 (1.77)	1.17 (1.34)
Current DMD, n (%)			
Interferon betas	18 (40)	15 (33.3)	8 (33.3)
Glatiramer Acetate	4 (8.9)	4 (8.9)	1 (4.2)
Teriflunomide	0 (0)	0 (0)	0 (0)
Fingolimod	6 (13.3)	8 (17.8)	7 (29.2)
Alemtuzumab	0 (0)	4 (8.9)	1 (4.2)
Dimethyl Fumarate	9 (20)	5 (11.1)	3 (12.5)
Natalizumab	7 (15.6)	8 (17.8)	4 (16.7)
Mitoxantrone	1 (2.2)	1 (2.2)	0 (0)

DMD, disease-modifying drugs; HAI = Hauser Ambulation Index; Experiments 2 and 3 have same patient groups

Table 8.2 Comparison of patients' assessment scores of numerical reasoning, health literacy, premorbid IQ and MS symptoms for Experiments, 1, 2, 3 and 4

Assessments	Max score	Mean scores (SD)		
		Exp 1 (n=45)	Exp 2 and 3 (n=45)	Exp 4 (n=24)
Numerical reasoning	25	16.20 (3.61)	16.36 (3.80)	16.63 (3.00)
Literacy	8	7.49 (1.25)	7.42 (1.32)	7.79 (.59)
Anxiety	21	7.51 (4.57)	6.27 (3.98)	6.88 (4.20)
Depression	21	5.02 (4.23)	4.11 (3.69)	5.38 (4.45)
Fatigue	63	42.64 (13.56)	44.00 (13.47)	44.71 (12.84)
Premorbid IQ	50	37.78 (6.86)	36.69 (8.46)	35.83 (8.02)
Info processing speed	110	57.07 (11.09)	56.62 (12.62)	63.79 (6.72)
Verbal memory	80	48.44 (14.08)	49.07 (12.43)	49.58 (9.82)
Visual memory	36	20.29 (6.99)	21.16 (6.46)	22.04 (6.08)

Experiments 2 and 3 have same patient groups

Table 8.3 Comparison of patients impaired on numerical reasoning, health literacy, premorbid IQ and MS symptoms for Experiments, 1, 2, 3 and 4

Assessments	Frequency of patients (%)		
	Exp 1 (n=45)	Exp 2 and 3 (n=45)	Exp 4 (n=24)
Numerical reasoning	3 (6.7)	6 (13.3)	2 (8.3)
Literacy	4 (8.9)	3 (6.7)	1 (4.2)
Anxiety	14 (31.1)	5 (11.1)	5 (33.3)
Depression	6 (13.3)	1 (2.2)	4 (16.7)
Fatigue	21 (46.7)	22 (48.9)	13 (54.2)
Premorbid IQ	1 (2.2)	3 (6.7)	1 (4.2)
Info processing speed	13 (28.9)	14 (31.1)	0 (0)
Verbal memory	15 (33.3)	15 (33.3)	7 (29.2)
Visual memory	25 (55.6)	23 (51.1)	10 (41.7)

Experiments 2 and 3 have same patient groups

With these limitations in mind, the efficacy of the BRIMMS protocol should be replicated in future studies. The BRIMMS protocol should be adopted and validated for use in a real clinical context with real DMD information and in consultations conducted by health professionals. This should especially be assessed in situations where patients are transitioning between DMDs, to examine whether the BRIMMS protocol can improve understanding when comparing between previously taken treatments to treatments that are new. Following this, a multicentre study evaluating the use of the BRIMMS protocol across the UK should be conducted. Along with understanding, these studies should also assess the best treatment decisions made by patients, by measuring patients' preferences for risks and benefits and comparing this with the risks and benefits of their chosen treatment following the BRIMMS protocol. Patients' decisions based on the BRIMMS protocol should also be followed up to evaluate whether improving understanding of treatment information via this protocol can increase adherence to treatment. Training should also be provided to MS nurses and neurologists on how to employ the BRIMMS protocol effectively during consultations (e.g. presenting the graphs visually if aural BRIMMS protocol is employed). Additionally, considering that health professionals also commonly direct patients to booklets and websites about DMDs following consultations (see chapter 3 and appendix 11), it may be possible to adapt the BRIMMS protocol for use in booklets and websites that patients could consult when deliberating about treatments beyond consultations. Future research should therefore evaluate the BRIMMS protocol in different formats to facilitate MS patients' understanding at all stages of the decision-making process. Following its use for MS patients, the BRIMMS protocol can also be validated and adopted for other chronic diseases that may have similar complex treatment risk-benefit profiles.

8.3 Conclusion

A theoretical framework was developed and tested to assess how MS patients' understanding of treatment information can be affected by different presentation methods and symptoms of MS. The effect of patient characteristics on understanding was also assessed. With evidence from reviews, surveys and empirical experiments in the current thesis, this theoretical framework was updated and used for the development of a BRIMMS protocol (see figure 6.2). According to this new framework, patients with cognitive impairments, poor numerical reasoning and poor premorbid IQ are susceptible to misunderstanding treatment information. Findings from Experiments 1-3 included in the framework also showed that all presentation methods had an impact on MS patients' understanding of treatment information. In particular, several best presentation methods were identified and include: bar charts, frequencies in the N-in-N*X ratios and clinical trial data communicated in absolute terms. The BRIMMS protocol was developed by integrating the best presentation methods and improved patient understanding of treatment information as well as reduced patients' conflict in their treatment decisions. Patient understanding was not directly related to decisional conflict across all experiments.

8.4 Clinical implications

Cognitive impairments should be assessed and accommodated as part of routine patient engagement and management, especially when discussing the risks and benefits of DMDs. Numerical reasoning and premorbid IQ are other patient characteristics that should be taken into account during treatment decisions. Education and discussion about DMD risks and benefits should be supported by using the best presentation methods such as frequencies, bar charts and absolute terms. BRIMMS protocol effectively integrates the best presentation methods and showed improvements in MS patients' understanding of

treatment risks and benefits. The BRIMMS protocol should therefore be validated in real clinical situations, before being implemented into clinical practice.

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Appendices

Appendix 1

Systematic review 1

Reen, G. K., Silber, E., & Langdon, D. W. (2017). Multiple sclerosis patients' understanding and preferences for risks and benefits of disease-modifying drugs: A systematic review. *Journal of the Neurological Sciences*, 375, 107–122.

Included as additional material

Appendix 2

Systematic review 2

Reen, G. K., Silber, E., & Langdon, D. W. (2017). Interventions to support risk and benefit understanding of disease-modifying drugs in Multiple Sclerosis patients: A systematic review. *Patient education and counseling*, 100(6), 1031-1048.

Included as additional material

Appendix 3

RHUL ethics approval

Ref: 2014/043 Ethics Form Approved



Psychology-Webmaster@rhul.ac.uk

Mon 17/11/2014, 11:28

pajt001@rhul.ac.uk; Langdon, D; PSY-EthicsAdmin@rhul.ac.uk; Zagefka, Hanna; uqjt005@rhul.ac.uk



Inbox

Application Details: View the form click [here](#) Revise the form click [here](#)

Applicant Name: **Gurpreet Reen**

Application title: **Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS)**

Comments: Approved.

Appendix 4

NHS ethics approval

NHS
Health Research Authority
NRES Committee South Central - Oxford C
Level 3, Block B
Whitefriars Building
Lewins Mead
Bristol
BS1 2NT
Telephone: 01173 421383

23 September 2014

Miss Gurpreet Reen
Department of Psychology
Royal Holloway, University of London
Egham
TW20 0EX

Dear Miss Reen

Study title:	Improving understanding and recall of risk information relating to MS medication: Developing an evidence-based clinical tool for assisting communication and understanding of MS medication risk information between patients and health professionals - Benefit and Risk information for Medication in Multiple Sclerosis (BRIMMS)
REC reference:	14/SC/1266
Protocol number:	N/A
IRAS project ID:	155057

Thank you for your letter responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Miss Lauren Allen, nrescommittee.southcentral-oxfordc@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the

A Research Ethics Committee established by the Health Research Authority

Appendix 4 continued



study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

A Research Ethics Committee established by the Health Research Authority

Appendix 4 continued



Health Research Authority

The documents reviewed and approved by the Committee are:

Document	Version	Date
Copies of advertisement materials for research participants [Advert for patient recruitment]	1	01 September 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Professional indemnity policy schedule]	1	01 September 2014
Interview schedules or topic guides for participants [Interview topic guides for MS Patients - 1.3]	1	03 September 2014
IRAS Checklist XML [Checklist_04092014]		04 September 2014
Letter from sponsor [Professional indemnity letter]	1	01 September 2014
Non-validated questionnaire [Survey questions - MS Nurses 1.1]	1	01 September 2014
Non-validated questionnaire [Survey questions - MS patients 1.2]	1	01 September 2014
Participant consent form [Consent form - Randomised Controlled Trial 1.5]	1	01 September 2014
Participant consent form [Consent form - Experiments 1-3 1.4]	1	01 September 2014
Participant consent form [Consent form - MS patient interviews 1.3]	1	01 September 2014
Participant consent form [Consent form - MS patient survey 1.2]	1	01 September 2014
Participant consent form [Consent form - MS Nurses survey 1.1]	1	01 September 2014
Participant information sheet (PIS) [Patient Survey]	2	23 September 2014
Participant information sheet (PIS) [MS Nurses Survey]	2	23 September 2014
Participant information sheet (PIS) [Randomised Controlled Trial]	2	23 September 2014
Participant information sheet (PIS) [Experiments 1-3]	2	23 September 2014
Participant information sheet (PIS) [Patient Interviews]	2	23 September 2014
REC Application Form [REC_Form_03092014]		03 September 2014
Research protocol or project proposal [BRIMMS Research protocol]	1	02 September 2014
Response to Request for Further Information [Covering Letter]		22 September 2014
Summary CV for Chief Investigator (CI) [CV Chief investigator - GR]	1	01 September 2014
Summary CV for supervisor (student research) [CV Academic supervisor - DL]	1	03 September 2014
Validated questionnaire [Fatigue Severity Scale (FSS)]	1	
Validated questionnaire [Hospital Anxiety Depression Scale]	1	01 September 2014
Validated questionnaire [Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) - BVMTR sub test]	1	
Validated questionnaire [Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) - CVLT sub test]	1	
Validated questionnaire [Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) - SDMT sub test]	1	
Validated questionnaire [Decisional Conflict Scale (DCS)]	1	

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

A Research Ethics Committee established by the Health Research Authority

Appendix 4 continued



After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance>

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

14/SC/1266	Please quote this number on all correspondence
------------	--

With the Committee's best wishes for the success of this project.

Yours sincerely

Mrs Susan Lousada

Chair

Email: nrescommittee.southcentral-oxfordc@nhs.net

Enclosures: *"After ethical review – guidance for researchers"*

Copy to: *Miss Gurpreet Reen*

Ms Sue Ormord, King's College Hospital NHS Foundation Trust

Appendix 4 continued



Date: 13/02/2015

NeuroRAG approval

Dear Miss Reen,

Thank you for completing the feasibility review and addressing previous issues for your study "BRIMMS"

"BRIMMS" was reviewed by both the Chair and Vice chair of the NeuroRAG committee. We would like to thank you for making the recommended changes to the recruitment changes and for confirming all funding arrangements. We would strongly recommend that you apply for portfolio adoption.

We would also like to extend our congratulations on gaining NeuroRAG approval.

With this clinical approval you can now move onto the next stage of the process which is to contact King's College Hospital Research and Development team for corporate approval.

The committee would like to extend their congratulations and the best of luck with your study.

Kind regards

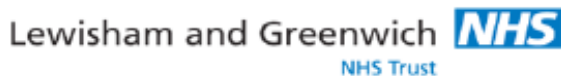
A handwritten signature in blue ink, appearing to read "K Ray Chaudhuri".

Prof. K Ray Chaudhuri
Chair

A handwritten signature in blue ink, appearing to read "K. Ashkan".

Prof. K. Ashkan
Vice Chair

Appendix 4 continued



Miss Gurpreet Reen
Royal Holloway, University of London
Egham
TW20 0EX

Research, Development & Innovation
4th Floor, Nockolds House
University Hospital Lewisham
Lewisham High Street
London
SE13 6LH
Email: lh.rd@nhs.net
Telephone: 0208 333 3000 ex 6361
6112

04th June 2015

Dear Miss Gurpreet Reen

Study Name: Improving understanding and recall of risk information relating to MS medication: Developing an evidence based clinical tool for assisting communication and understanding of MS medication risk information between patients and health professionals
Benefit and Risk information for Medication in Multiple Sclerosis (BRIMMS)

REC ref: 14/SC/1266
IRAS: 155057
R&D: 155057 QEH

We are pleased to inform you that you have been granted Trust R&D approval for the above study.

The following documents have been reviewed:

Document	Version	Date
Participant consent form [Consent form - Randomised Controlled Trial 1.5]	1	01 September 2014
Participant consent form [Consent form - Experiments 1-3 1.4]	1	01 September 2014
Participant consent form [Consent form - MS patient interviews 1.3]	1	01 September 2014
Participant consent form [Consent form - MS patient survey 1.2]	1	01 September 2014
Participant consent form [Consent form - MS Nurses survey 1.1]	1	01 September 2014
Participant information sheet (PIS) [Patient Survey]	2	23 September 2014
Participant information sheet (PIS) [MS Nurses Survey]	2	23 September 2014
Participant information sheet (PIS) [Randomised Controlled	2	23 September 2014

Lewisham and Greenwich R&D Approval Template 2014 V2

Appendix 4 continued

Trial]		
Participant information sheet (PIS) [Experiments 1-3]	2	23 September 2014
Participant information sheet (PIS) [Patient Interviews]	2	23 September 2014
REC Application Form [REC_Form_03092014]	03 September 2014	
Research protocol or project proposal [BRIMMS Research protocol]	1	02 September 2014

NHS permission is granted on the understanding and provision that you adhere to the following conditions:

- The research is conducted in line with the Department of Health Research Governance Framework for Health and Social Care (Second Edition April 2005), The Data Protection Act 1998, the Human Tissue Act 2004 and the Medicines for Human Use (Clinical Trials) Regulations 2004.
- The research is conducted to the approved protocol and in accordance with Trust policies and procedures.
- All amendments to the approved project must be approved by the Ethics Committee and copies provided to the R&D Office for approval, and where necessary approval is obtained before the changes are implemented
- Please also ensure that the office is notified of any changes in status to the project, for example if the site should close before the stated end date and any urgent safety measures enacted.
- You must notify the R&D Office of the actual commencement and completion date of the study.
- Co-operate with monitoring and auditing when required for compliance against the standards set out in the Research Governance Framework. You will be notified by the R&D Office if and when your project has been selected for monitoring.
- Recruitment figures are reported to the R&D department when requested on a monthly basis
- Date of first patient recruited must be reported to the R&D office, using the reply slip attached.

As part of research governance, it is your responsibility to report any adverse or health and safety events that happen as a result of the study to the R&D department. It is also your responsibility as the Trust lead for this project to ensure that all staff involved with the project are adequately trained.

Appendix 4 continued

Please note that this approval is only valid until the project end date that has been provided.

We will make contact with you on a regular basis for recruitment updates. If you require any assistance from the R&D Department please do not hesitate to contact us.

Yours sincerely

A handwritten signature in black ink that reads "Parchment". The signature is written in a cursive style with a large, stylized 'P'.

Carlene Parchment
R&D Manager

Cc: Dr Silber, Consultant Neurologist, QEH

Appendix 5

MS Patient survey



Are you currently taking a disease-modifying medication for MS?

Yes ☐ No ☐

If you answered NO, please DO NOT complete this survey.

If you answered YES, please continue to the next question.

Please tell us the medication you are **currently** taking?

Avonex	<input type="checkbox"/>	Betaferon	<input type="checkbox"/>	Copaxone	<input type="checkbox"/>
Extavia	<input type="checkbox"/>	Aubagio	<input type="checkbox"/>	Gilenya	<input type="checkbox"/>
Lemtrada	<input type="checkbox"/>	Rebif	<input type="checkbox"/>	Tecfidera	<input type="checkbox"/>
				Tsyabri	<input type="checkbox"/>

How long have you been taking your **current** medication?

We are interested to know how well you feel you are aware of the side effects, risks and benefits of your current medication.

- How well do you feel you understand the benefits of your current medication? Please tick one.

Slightly understood	Moderately understood	Satisfactorily understood	Very well understood	Completely understood
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments: _____

Appendix 5 continued



We are interested to know how well you feel you are aware of the side effects, risks and benefits of your current medication.

2. How well do you feel you understand the benefits of your current medication? Please tick one.

Slightly Understand	Moderately understand	Satisfactorily understand	Very well understand	Completely understand
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments:

3. How well do you feel you understand the side-effects of your current medication? Please tick one.

Slightly Understand	Moderately understand	Satisfactorily understand	Very well understand	Completely understand
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments:

4. How well do you feel you understand the significant risks of your current medication?

Please tick one.

Slightly understood	Moderately understood	Satisfactorily understood	Very well understood	Completely understood
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments:

Appendix 5 continued



5. What source of information about risks and benefits for your current medication do you currently use?

Please tick all that apply.

- MS Neurologist ☐ MS Nurses ☐ Booklet ☐
 Charity website (*e.g. MS Trust/MS Society*) ☐
 Patient website (*e.g. Shift MS/Patients Like Me*) ☐
 App (*phone or tablet*) ☐ Video guide (DVD/YouTube) ☐
 Other ☐ If other, please specify:

6. How useful are the sources you have stated in your previous answer, in providing you with risk and benefit information of your current medication?

7. What source of information about risks and benefits for your current medication, do you currently prefer to use or would prefer to use in the future?

Please rate these choices from 1 to 7, where 1 is your MOST preferred source and 7 is your LEAST preferred choice.

MS Neurologist _____

MS Nurses _____

Booklet _____

Charity website (*e.g. MS Trust/MS Society*) _____

Patient website (*e.g. Shift MS/Patients Like Me*) _____

App (*phone or tablet*) _____

Video guide (DVD/YouTube) _____

Comments:

Appendix 5 continued



8. How can the current way of providing risk and benefit information for your current medication be improved?

9. On average, how often do you receive information about the benefits, risks and side-effects about your current medication:

Every consultation ☐ 1 in 2 consultations ☐

1 in 5 consultations ☐ 1 in 10 consultations ☐

In less than 1 in 10 consultations ☐

Comments:

10. What do you think the possible benefits of your current medication are for MS patients?

11. What do you think the possible side-effects of your current medication are for MS patients?

12. What do you think the possible significant risks of your current medication are for MS patients?

Appendix 5 continued



13. What benefits have you experienced from your current medication, if any?

14. What side-effects have you experienced from your current medication, if any?

Thank you for completing this survey! Your answers will help us understand and improve the way risk and benefit information is presented to people with MS.

Please return your completed survey by post using the envelope provided or hand this back to the researcher.

You may also complete the survey online at: www.tinyurl.com/MS-DMD-survey

Appendix 6

MS Nurse surveys



Have you had a consultation with at least one MS patient: Yes ☐ No ☐

Please DO NOT complete the survey if you responded No.

How long have you been a MS nurse? _-

We are interested to know how well you feel side effects, risks and benefits of disease-modifying drugs (DMDs) are understood by MS patients.

15. How well do you feel benefits of DMDs are understood by MS patients?

Please tick one.

Slightly understood	Moderately understood	Satisfactorily understood	Very well understood	Completely understood
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments:

16. How well do you feel side-effects of DMDs are understood by MS patients?

Please tick one.

Slightly understood	Moderately understood	Satisfactorily understood	Very well understood	Completely understood
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments:

Appendix 6 continued



17. How well do you feel significant risks of DMDs are understood by MS patients?
Please tick one.

Slightly understood	Moderately understood	Satisfactorily understood	Very well understood	Completely understood
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments:

18. What sources of information about risks and benefits of medication do patients use?
Please tick all that apply.

MS Neurologist	<input type="checkbox"/>	MS Nurses	<input type="checkbox"/>	Booklet	<input type="checkbox"/>
Charity website (e.g. MS Trust/MS Society)	<input type="checkbox"/>				
Patient website (e.g. Shift MS/Patients Like Me)	<input type="checkbox"/>				
App (phone or tablet)	<input type="checkbox"/>	Video guide (DVD/YouTube)	<input type="checkbox"/>		

Other ☐ If other, please specify: -

19. How useful are the sources you have stated in your previous answer, in providing MS patients with medication risk and benefit information?

20. How can the current way of providing medication risk and benefit information be improved?

Appendix 6 continued



21. On average, do you discuss medication benefits, risks and side-effects with patients:

- Every consultation ☐ 1 in 2 consultations ☐
- 1 in 5 consultations ☐ 1 in 10 consultations ☐
- In less than 1 in 10 consultations ☐

Comments:

Thank you for completing this survey! Your answers will help us understand and improve the way risk and benefit information is presented to people with MS.

Please return your completed survey by post using the envelope provided or you can hand this back to the researcher.

You also may complete the survey online at: www.tinyurl.com/MS-nurse-survey

Appendix 7

Information sheet and consent form for MS patient surveys



Participant information Sheet:

Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS)

Survey

We would like to invite you to take part in our research study. This research study is being conducted as part of a PhD project at Royal Holloway, University of London. Before you decide to take part we would like you to understand why the research is being done and what it would involve for you. Please take the time to read the following information carefully and discuss it with others if you wish. Please do not hesitate to contact us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part in this research study.

What is the purpose of this study?

We are conducting this study to look at how information about risks and benefits of medication is currently presented to people with MS. We are hoping this will help us identify how this information can be presented in the most effective way.

Why have I been invited to take part?

People who have been diagnosed with Multiple Sclerosis and are currently taking disease-modifying drugs (DMDs) have been invited to take part. We are surveying about 100 patients from many different medication groups.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide not to, it will in no way affect the care you receive. If you decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form. Even if you do agree to participate you may withdraw at any time without giving a reason.

Appendix 7 continued**What will I have to do?**

The risk and benefit profile of disease-modifying medications are complex and not always easy to understand and remember. We would like to find out the best way of providing information about the risks and benefits of disease-modifying medications to people with MS.

To do this, we would like to survey people with MS about their experience of receiving risk and benefit information about their medication and their current level of awareness. We would also like to find out the sources that people with MS currently use for information about medication risks and benefits and how these could be improved.

The surveys may be completed at your convenience and will take no longer than 30 minutes of your time. Once completed, you may personally hand these to the research team or can post them using the envelopes provided. Your answers to all the questions will provide us with the best information, but you may choose to leave out any questions that you do not wish to answer without giving a reason. If you are uncomfortable or unsure of a question, you may wish to contact your MS Nurse or Doctor at any point to discuss this.

What are the possible benefits of taking part?

We cannot promise that taking part in this study will help you, but the information we get from this study will help improve the risk and benefit information that people with Multiple Sclerosis receive about medications.

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research study will be kept strictly confidential and will only be viewed by authorised researchers in the research team. All data that is used beyond the research institution will be coded and anonymised, so you will not be identified.

Appendix 7 continued



What will happen to the results of the study?

If the results of the study are published, participants will be kept anonymous and will not be identified in any reports or publication.

Any direct quotations used from the study will be kept completely anonymous.

Who is organising and funding the research?

The research is being funded by Royal Holloway, University of London and a pharmaceutical company named Biogen Idec Limited.

Who has reviewed the study?

This research study is part of the NHS and has been looked at by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by South Central Oxford C Research Ethics Committee.

The research has also been approved by the Ethics Committee at Royal Holloway, University of London.

Contact details

If you have any questions about the survey or would like more information about this research project, please contact:

Miss Gurpreet Reen - Royal Holloway, University of London

Email: gurpreet.reen.2014@live.rhul.ac.uk

Telephone: 0787 845 1844

Appendix 7 continued



Consent form

Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS)

Survey

1. I confirm that I have read and understood the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected. ☐
3. I agree to take part in the above study. ☐

Name of Participant

Date

Signature

Appendix 8

Information sheet and consent form for offline MS nurse surveys



Participant information Sheet:

Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS)

MS Nurses Survey

We would like to invite you to take part in our research study. This research study is being conducted as part of a PhD project at Royal Holloway, University of London. Before you decide to take part we would like you to understand why the research is being done and what it would involve for you. Please take the time to read the following information carefully and discuss it with others if you wish. Please do not hesitate to contact us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part in this research study.

What is the purpose of this study?

We are conducting this study to look at how information about risks and benefits of medication is presented to people with MS. At the end of the project we will have identified how this information can be presented in the most effective way.

Why have I been invited to take part?

MS Nurses, who work with patients with Multiple Sclerosis, have been invited to take part. We are hoping to recruit about 50 MS Nurses in the next few months.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. Even if you do agree to participate you may withdraw at any time without giving a reason.

Appendix 8 continued**What will I have to do?**

Sometimes, we don't know how much people with MS are aware of the risks and benefits of their current medication and whether they would like more information about MS, their current medications and any side-effects and benefits they may experience from their current treatment.

To find out, we would like to survey MS nurses regarding their experience about medication risks and benefits information that is provided to people with MS, and the different sources that patients use to obtain this information. We would also like to know how MS nurses think that the medication risk and benefit information can be improved. This will help us understand and improve the way risk and benefit information is presented to people with MS.

The survey may be completed at your convenience and will take no longer than 30 minutes of your time. Once completed, you may personally hand these to the research team or can post them using the envelopes provided. Your answers to all the questions will provide us with the best information, but you may choose to leave out any questions that you do not wish to answer without giving a reason.

What are the possible benefits of taking part?

We cannot promise that taking part in this study will help you, but the information we get from this study will help improve the risk and benefit information that people with Multiple Sclerosis receive about medications.

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research study will be kept strictly confidential and will only be viewed by authorised researchers in the research team. All data that is used beyond the research institution will be coded and anonymised, so you will not be identified.

What will happen to the results of the study?

If the results of the study are published, participants will be kept anonymous and will not be identified in any reports or publication.

Any direct quotations used from the study will be kept completely anonymous.

Appendix 8 continued



Who is organising and funding the research?

The research is being funded by Royal Holloway, University of London and a pharmaceutical company named Biogen Idec Limited.

Who has reviewed the study?

This research study is part of the NHS and has been looked at by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by South Central Oxford C Research Ethics Committee.

The research has also been approved by the Ethics Committee at Royal Holloway, University of London.

Contact details

If you have any questions about the survey or would like more information about this research project, please contact:

Miss Gurpreet Reen - Royal Holloway, University of London

Email: gurpreet.reen.2014@live.rhul.ac.uk

Telephone: 07563 653799

Appendix 8 continued



Consent form

Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS)

MS Nurses Survey

1. I confirm that I have read and understood the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and legal rights being affected. ☐
3. I agree to take part in the above study. ☐

Name of Participant

Date

Signature

Appendix 9

Information and consent for online MS patient surveys

Survey of people with MS

We would like to invite you to take part in our research study by completing this survey. This research study is being conducted as part of a PhD project at Royal Holloway, University of London.

We hope to find out the best way of providing information about the risks and benefits of disease-modifying medications to people with MS. To do this, we would like to survey people with MS about their experience of receiving risk and benefit information about their medication and their current level of awareness.

We would also like to find out the sources that people with MS currently use for information about medication risks and benefits and how these could be improved.

By continuing onto the next screen, you are deemed to have given consent to participate in this research. This is an anonymous survey. Please do not enter your name or any personal details that could identify you.

If you are happy to take part in this survey, please continue to the next page.

Appendix 10

Information and consent for online MS nurse surveys

We would like you to take part in our research study by completing this survey. This research study is being conducted as part of PhD project at Royal Holloway, University of London.

We hope to find out the best way of providing information about the risks and benefits of disease-modifying medications to people with MS. To do this, we would like to survey MS Nurses regarding their experience about medication risk and benefit information that is provided to people with MS, and the different sources that patients use to obtain this information. We would also like to know how MS Nurses think the medication risk and benefit information for people with MS can be improved.

By continuing onto the next screen, you are deemed to have given consent to participate in this research. This is an anonymous survey. Please do not enter your name or any personal details that could identify you.

If you are happy to take part in this survey, please continue to the next page.

Appendix 11

Example of DMD risks and benefits presented within an online and offline booklet produced by the charity MS Trust (with annotations)



Appendix 11 continued

How effective are disease modifying drugs?

Large scale clinical trials compare the number of relapses in people taking a new drug with those taking an existing DMD or placebo (dummy drug). Trials may also measure the number of lesions seen on MRI scans and changes in disability which last for 3 months or longer.

Data from trials can be used to group the DMDs according to how effective they are. In this guide, we've followed broad categories recommended in guidelines published by the Association of British Neurologists (ABN):

- Category 1.1: **moderately effective** - reduces relapses by one third (30%)
- Category 1.2: **more effective** - reduces relapses by one half (50%)
- Category 2.0: **highly effective** - reduces relapses by two thirds (70%)

*Verbal
format*

*Relative risk
reduction*

*Verbal
format*

*Frequency
1-in-X ratio*

Avonex, Betaferon, Extavia, Plegridy, Rebif

Common side effects (affecting more than 1 person in 100)

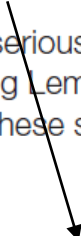
- flu-like symptoms
- injection site reactions
- headache
- decrease in white blood cells
- difficulty sleeping
- diarrhoea, nausea and vomiting
- depression
- hair loss

Appendix 11 continued**Lemtrada**

Three serious side effects have been reported from clinical trials:

- overactive or underactive thyroid gland leading to thyroid disorders, affecting 300 in 1000 people
- idiopathic thrombocytopenic purpura (ITP), a serious disorder which prevents blood from clotting, affecting 10 in 1000 people
- kidney problems, affecting 3 in 1000 people

These side effects are potentially serious but they are treatable if caught early enough. People taking Lemtrada will be informed of the early signs and symptoms of these side effects.



*Frequency in
N-in-N*X ratio*

Appendix 12

Example of one hypothetical disease shown to patients in Experiment 1

Septhitus

The following information is about a fictitious medical disease, Septhitus, which is a chronic medical condition (a progressive condition) and leads to inflammation or erosion of the lining of the stomach.

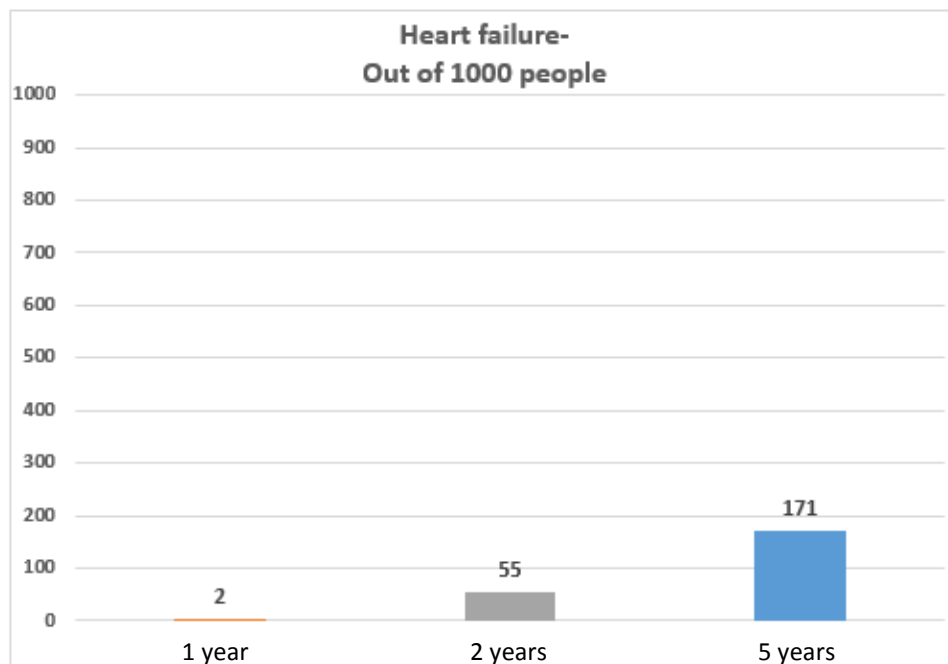


Without any treatment, the most common symptoms of the condition are:

- Disabling abdominal pain: Episodes of disabling pain will become frequent over time
- High blood pressure: People will be required to take medications for this condition
- Likely to develop Irritable Bowel Syndrome (IBS) soon after diagnosis: If diagnosed, people will be advised to avoid certain types of food to manage the condition
- Inability to digest solid food: In the severe form of the disease, people will need to go on a liquid diet.
- Development of nodules in the stomach: People with this disease go on to develop nodules in the abdomen which can be identified by scans. These nodules can cause severe complications and can be fatal. Surgery is required to remove nodules.

Appendix 13

Example of presentation formats and comprehension questions presented with Treatment A (Difoxitin) in Experiment 1

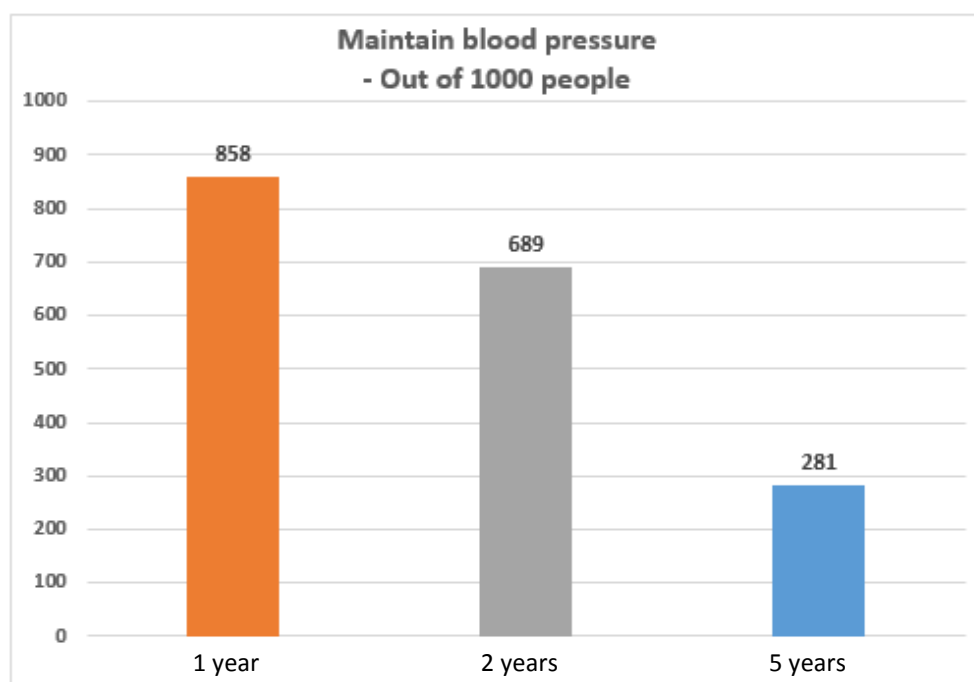


If 1000 people took Difoxitin for 1 year, how many people will have a risk of heart failure?

If 1000 people took Difoxitin for 2 years, how many people will have a risk of heart failure?

If 1000 people took Difoxitin for 5 years, how many people will have a risk of heart failure?

Appendix 13 continued

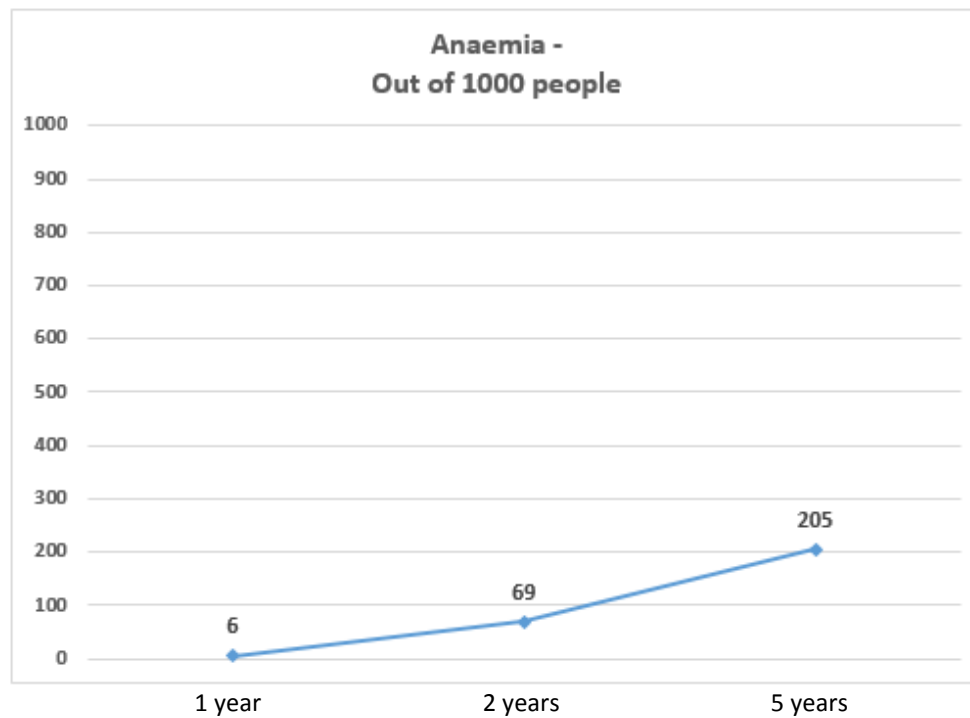


If 1000 people took Difoxitin for 1 year, how many people will maintain a normal blood pressure?

If 1000 people took Difoxitin for 2 years, how many people will maintain a normal blood pressure?

If 1000 people took Difoxitin for 5 years, how many people will maintain a normal blood pressure?

Appendix 13 continued

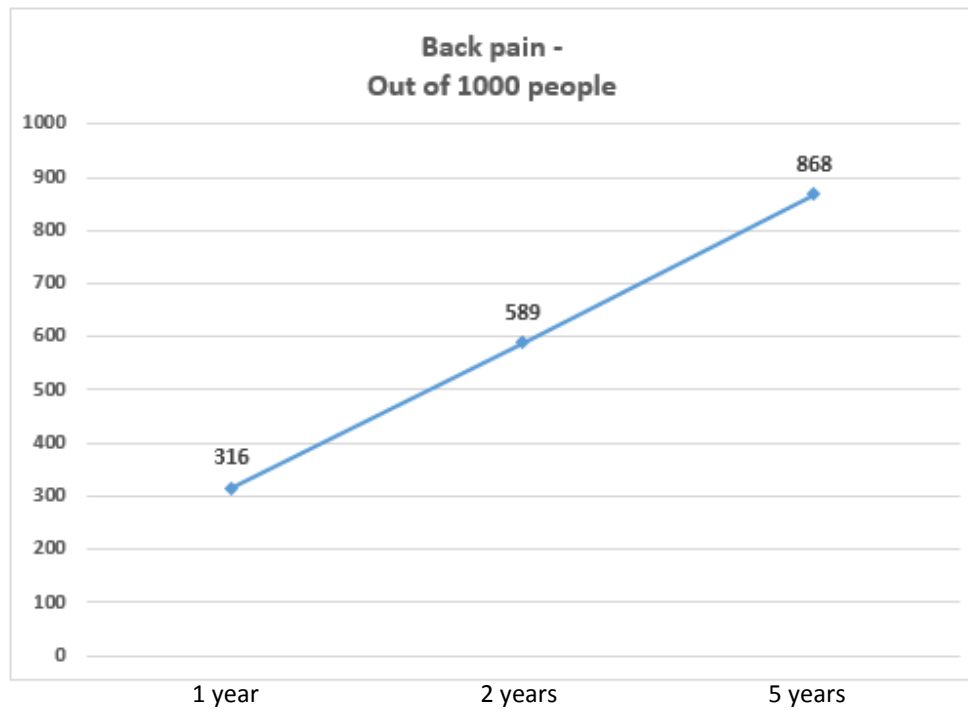


If 1000 people took Difoxitin for 1 year, how many people will develop anaemia?

If 1000 people took Difoxitin for 2 years, how many people will develop anaemia?

If 1000 people took Difoxitin for 5 years, how many people will develop anaemia?

Appendix 13 continued



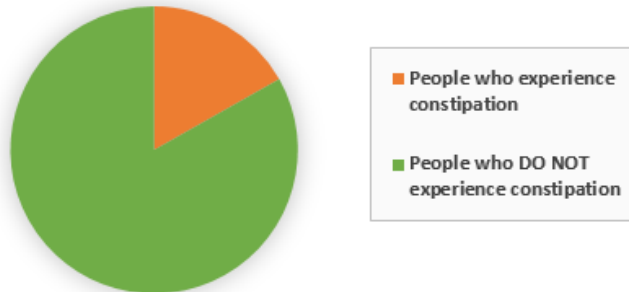
If 1000 people took Difoxitin for 1 year, how many people will experience back-pain?

If 1000 people took Difoxitin for 2 years, how many people will experience back-pain?

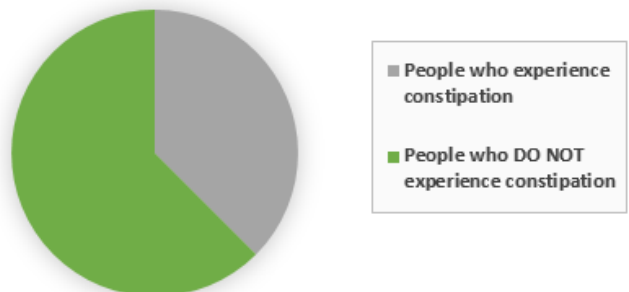
If 1000 people took Difoxitin for 5 years, how many people will experience back-pain?

Appendix 13 continued

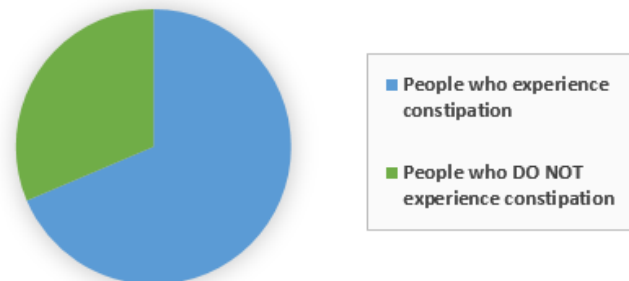
**Constipation after 1 year -
Out of 1000 people**



**Constipation after 2 years -
Out of 1000 people**



**Constipation after 5 years -
Out of 1000 people**



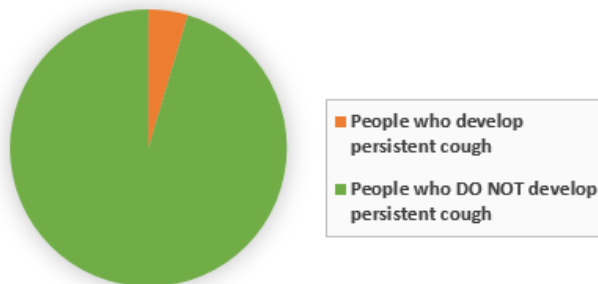
If 1000 people took Difoxitin for 1 year, how many people would experience constipation?

If 1000 people took Difoxitin for 2 years, how many people would experience constipation?

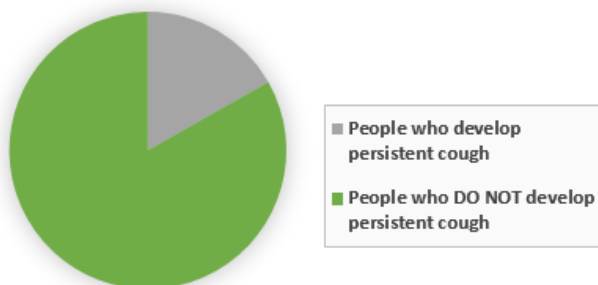
If 1000 people took Difoxitin for 5 years, how many people would experience constipation?

Appendix 13 continued

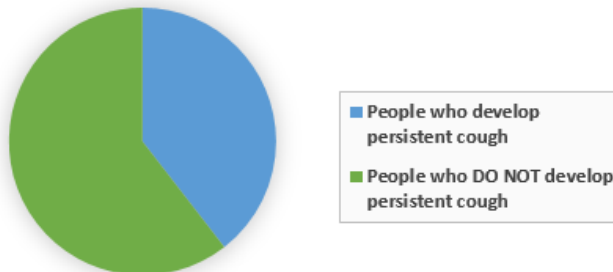
**Persistent cough after 1 year -
Out of 1000 people**



**Persistent cough after 2 years -
Out of 1000 people**



**Persistent cough after 5 years -
Out of 1000 people**

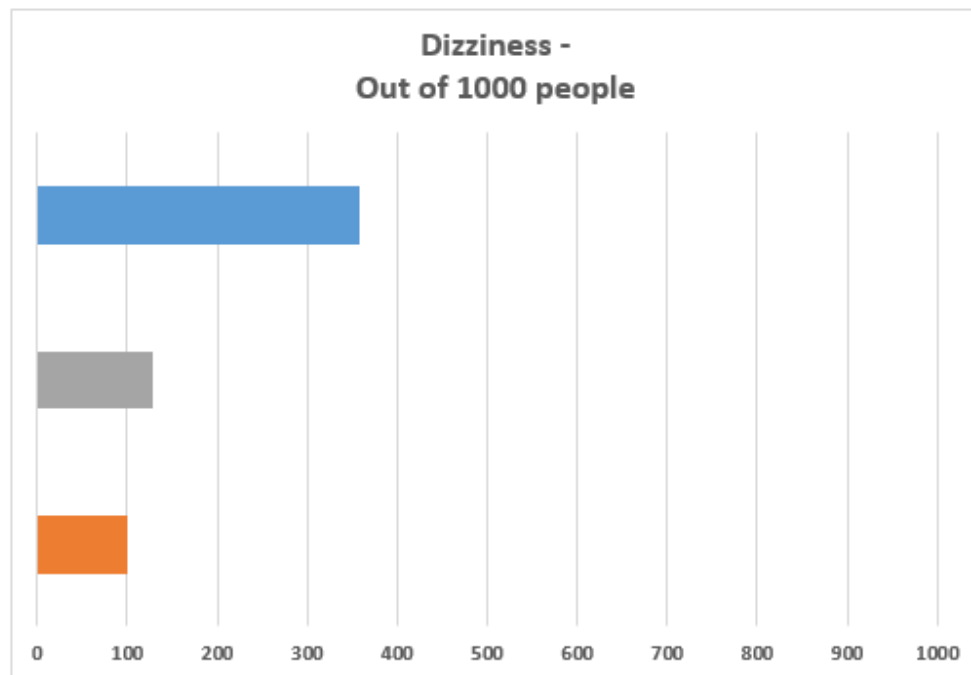


If 1000 people took Difoxitin for 1 year, how many people will develop persistent cough?

If 1000 people took Difoxitin for 2 years, how many people will develop persistent cough?

If 1000 people took Difoxitin for 5 years, how many people will develop persistent cough?

Appendix 13 continued

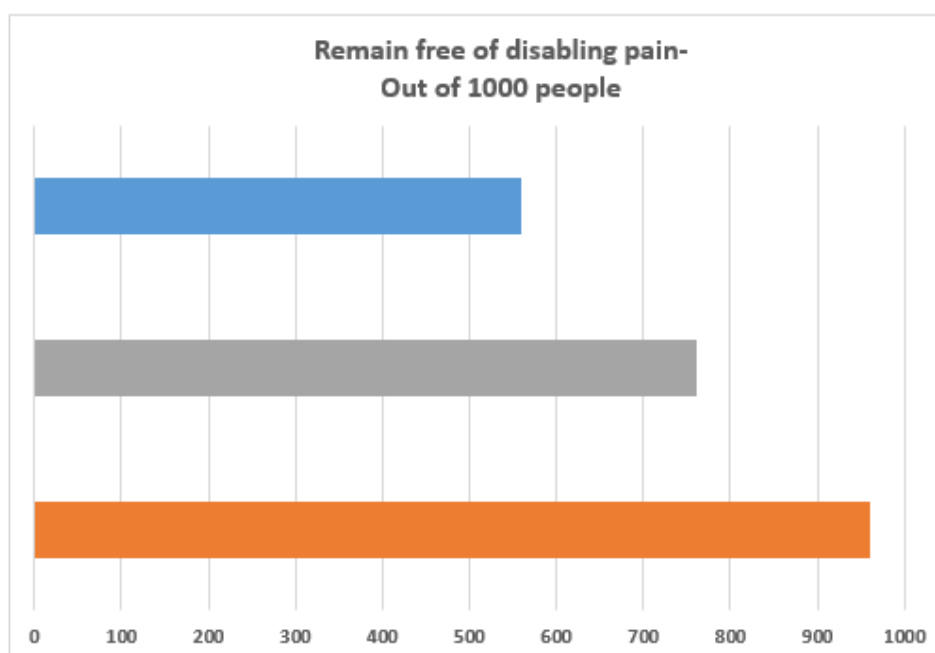


If 1000 people took Difoxitin for 1 year, how many people will experience dizziness?

If 1000 people took Difoxitin for 2 years, how many people will experience dizziness?

If 1000 people took Difoxitin for 5 years, how many people will experience dizziness?

Appendix 13 continued



If 1000 people took Difoxitin for 1 year, how many people will remain free of disabling pain?

If 1000 people took Difoxitin for 2 years, how many people will remain free of disabling pain?

If 1000 people took Difoxitin for 5 years, how many people will remain free of disabling pain?

Appendix 14

Information sheet and consent form for Experiments 1, 2 and 3



Participant information Sheet:

Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS)

Investigation of presentation of information

We would like to invite you to take part in our research study. This research study is being conducted as part of a PhD project at Royal Holloway, University of London. Before you decide to take part we would like you to understand why the research is being done and what it would involve for you. Please take the time to read the following information carefully and discuss it with others if you wish. One of our team will go through the information sheet with you and answer any questions you have, so ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?

We are conducting this study to look at how information about risks and benefits of medication is best presented to people with MS.

Why have I been invited to take part?

People who have been diagnosed with Multiple Sclerosis and are currently taking disease-modifying drugs (DMDs) have been invited to take part. We are hoping to recruit about 400 patients in total in the next 3 years.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide not to, it will in no way affect the care you receive. If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. Even if you do agree to participate you may withdraw at any time without giving a reason.

Appendix 14 continued**What will I have to do?**

Sometimes, we don't know how best to present risk and benefit information of medications to people with MS. This study will investigate which presentations best allow patients to understand and remember the information.

During this study, you will be shown information about risks and benefits of pretend drugs in many different formats. You will then be asked about the information and we will see how well you are able to remember this information.

Before the study task, you may also be required to fill in some questionnaires to find out some background information about you and your clinical history. You will also be requested to complete a few questionnaire and tasks which will inform us about your mood, fatigue, as well as memory and concentration.

The whole session may take around 1 to 2 hours. However, breaks will be given throughout the study and if at any point you feel uncomfortable or tired, you may also ask for additional breaks. You will receive further information throughout the study but if you require additional help or clarification you may let us know at any time. If you feel uncomfortable at any point in the study, you can stop at any time and you may also wish to contact your MS Nurse or Doctor to discuss this.

You may wish to be involved in more than one study session. If this is the case, we will arrange a mutually convenient time and you will be presented with this information sheet and consent form again at the start of each new visit.

Where will the study take place?

You may choose to be involved in the study at the hospital or in your own home. The study will be conducted by a member of the research team.

What are the possible benefits of taking part?

We cannot promise that taking part in this study will help you, but the information we get from this study will help improve the risk and benefit information that people with Multiple Sclerosis receive about medications.

Appendix 14 continued



Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research study will be kept strictly confidential and will only be viewed by authorised researchers in the research team. All data that is used beyond the research institution will be coded and anonymised, so you will not be identified.

What will happen to the results of the study?

If the results of the study are published, participants will be kept anonymous and will not be identified in any reports or publication.
Any direct quotations used from the study will be kept completely anonymous.

Who is organising and funding the research?

The research is being funded by Royal Holloway, University of London and a pharmaceutical company named Biogen Idec Limited.

Who has reviewed the study?

This research study is part of the NHS and has been looked at by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by South Central Oxford C Research Ethics Committee.

The research has also been approved by the Ethics Committee at Royal Holloway, University of London.

Contact details

If you have any questions about this study or would like more information about this research project, please contact:

Miss Gurpreet Reen - Royal Holloway, University of London

Email: gurpreet.reen.2014@live.rhul.ac.uk

Telephone: 0787 845 1844

Appendix 14 continued



Consent form

Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS)

Investigation of presentation of information

1. I confirm that I have read and understood the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected.

☐

3. I agree to take part in the above study.

☐

Name of Participant

Date

Signature

Appendix 15

Example of hypothetical disease shown to patients in Experiment 2

Tryken's disease

The following information is about a fake medical disease, Tryken's Disease, which is a chronic medical condition (a progressive condition) and leads to muscle wastage.



Without any treatment, the most common symptoms of the condition are:

- Severe weight loss: Over time, weight loss can be quite severe and will be difficult to manage
- Unusual and unexpected bruising: This could become frequent over time, and could develop on any parts of the body
- Muscle pain: The pain would require medications to manage and could result in frequent time off work
- Kidney failure: In the very severe form of the disease, patients could develop kidney failure and may require dialysis

Appendix 16

Example of ratios and framing to present information about treatment A (Sprantil) in Experiment 2

Appendicitis needing surgery after 1 year

In a clinical trial, 101 out of every 1000 people on *Sprantil* developed appendicitis requiring surgery after 1 year, and 899 out of every 1000 people did NOT develop appendicitis requiring surgery.

In the no-treatment group (placebo group), 12 out of every 1000 people developed appendicitis requiring surgery after 1 year, and 988 out of 1000 people did NOT develop appendicitis requiring surgery.

1. If 1000 people took *Sprantil* for 1 year, how many people will develop appendicitis requiring surgery?
2. Compared to the placebo group, approximately how many **MORE** people taking *Sprantil* will develop appendicitis after 1 year?
☐ 100 ☐ 300 ☐ 400 ☐ 750

Appendicitis needing surgery after 2 years

In a clinical trial, 176 out of every 1000 people on *Sprantil* developed appendicitis requiring surgery after 2 years, and 824 out of every 1000 people did NOT develop appendicitis requiring surgery.

In the no-treatment group (placebo group), 41 out of every 1000 people developed appendicitis requiring surgery after 2 years, and 959 out of 1000 people did NOT develop appendicitis requiring surgery.

1. If 1000 people took *Sprantil* for 2 years, how many people will develop appendicitis requiring surgery?

Appendix 16 continued

2. Compared to the placebo group, approximately how many **MORE** people taking *Sprantil* will develop appendicitis after 2 years?

☐ 150 ☐ 250 ☐ 450 ☐ 800

Appendicitis needing surgery after 5 years

In a clinical trial, 301 out of every 1000 people on *Sprantil* developed appendicitis requiring surgery after 5 years, and 699 out of every 1000 people did NOT develop appendicitis requiring surgery.

In the no-treatment group (placebo group), 53 out of every 1000 people developed appendicitis requiring surgery after 5 years, and 947 out of 1000 people did NOT develop appendicitis requiring surgery

1. If 1000 people took *Sprantil* for 5 years, how many people will develop appendicitis requiring surgery?
2. Compared to the placebo group, approximately how many **MORE** people taking *Sprantil* will develop appendicitis after 5 years?

☐ 150 ☐ 250 ☐ 400 ☐ 750

Bleeding gums after 1 year

In a clinical trial, 593 people out 1000 people on *Sprantil* did NOT develop bleeding gums after 1 year, compared to 929 out of 1000 people who did not take the treatment (placebo group).

If 1000 people took *Sprantil* for 1 year, how many people will NOT develop bleeding gums?

Compared to the placebo group, approximately how many **FEWER** people taking *Sprantil* will NOT develop bleeding gums after 1 year?

☐ 100 ☐ 200 ☐ 350 ☐ 800

Appendix 16 continued***Bleeding gums after 2 years***

In a clinical trial, 379 people out 1000 people on Sprantil did NOT develop bleeding gums after 2 years, compared to 880 out of 1000 people who did not take the treatment (placebo group).

1. If 1000 people took Sprantil for 2 years, how many people will NOT develop bleeding gums?
2. Compared to the placebo group, approximately how many **FEWER** people taking Sprantil will NOT develop bleeding gums after 2 years?

☐ 300 ☐ 500 ☐ 650 ☐ 750

Bleeding gums after 5 years

In a clinical trial, 301 people out 1000 people on Sprantil did NOT develop bleeding gums after 5 years, compared to 643 out of 1000 people who did not take the treatment (placebo group).

1. If 1000 people took Sprantil for 5 years, how many people will NOT develop bleeding gums?
2. Compared to the placebo group, approximately how many **FEWER** people taking Sprantil will NOT develop bleeding gums after 5 years?

☐ 150 ☐ 350 ☐ 600 ☐ 750

Appendix 16 continued***Remain free of unexpected bruising after 1 year***

In a clinical trial, 925 people out 1000 people on Sprantil will remain free of unexpected bruising after 1 year, compared to 410 out of 1000 people who did not take the treatment (placebo group).

1. If 1000 people took *Sprantil* for 1 year, how many people will remain free of unexpected bruising?
2. Compared to the placebo group, approximately how many **MORE** people taking *Sprantil* will remain free of unexpected bruising after 1 year?

☐ 350 ☐ 500 ☐ 700 ☐ 800

Remain free of unexpected bruising after 2 years

In a clinical trial, 870 people out 1000 people on Sprantil will remain free of unexpected bruising after 2 years, compared to 215 out of 1000 people who did not take the treatment (placebo group).

1. If 1000 people took *Sprantil* for 2 years, how many people will remain free of unexpected bruising?
2. Compared to the placebo group, approximately how many **MORE** people taking *Sprantil* will remain free of unexpected bruising after 2 years?

☐ 100 ☐ 450 ☐ 650 ☐ 900

Remain free of unexpected bruising after 5 years

In a clinical trial, 750 people out 1000 people on Sprantil will remain free of unexpected bruising after 5 years, compared to 100 out of 1000 people who did not take the treatment (placebo group).

1. If 1000 people took *Sprantil* for 5 years, how many people will remain free of unexpected bruising?
2. Compared to the placebo group, approximately how many **MORE** people taking *Sprantil* will remain free of unexpected bruising after 5 years?

☐ 50 ☐ 200 ☐ 350 ☐ 650

Appendix 16 continued***Remain free of kidney failure after 1 year***

In a clinical trial, around 1 out of every 1 person on Sprantil remained free of kidney failure after 1 year, compared to 1 out of every 2 people who did not take the treatment (placebo group).

1. If 1000 people took *Sprantil* for 1 year, how many people will remain free of kidney failure?
2. Compared to the placebo group, approximately how many **MORE** people taking *Sprantil* will remain free of kidney failure after 1 year?

☐ 250 ☐ 450 ☐ 700 ☐ 800

Remain free of kidney failure after 2 years

In a clinical trial, around 1 out of every 1 person on Sprantil remained free of kidney failure after 2 years, compared to 1 out of every 3 people who did not take the treatment (placebo group).

1. If 1000 people took *Sprantil* for 2 years, how many people will remain free of kidney failure?
2. Compared to the placebo group, approximately how many **MORE** people taking *Sprantil* will remain free of kidney failure after 2 years?

☐ 250 ☐ 500 ☐ 600 ☐ 850

Remain free of kidney failure after 5 years

In a clinical trial, around 1 out of every 2 people on Sprantil remained free of kidney failure after 5 years, compared to 1 out of every 4 people who did not take the treatment (placebo group).

1. If 1000 people took *Sprantil* for 5 years, how many people will remain free of kidney failure?
2. Compared to the placebo group, approximately how many **MORE** people taking *Sprantil* will remain free of kidney failure after 5 years?

☐ 200 ☐ 350 ☐ 700 ☐ 800

Appendix 17

Example of hypothetical disease shown to patients in Experiment 3

Aortic Prithora

The following information is about a fake medical disease, Aortic Prithora, which is a chronic medical condition (a progressive condition) and leads to complications of the heart.



Without any treatment, the most common symptoms of the condition are:

High cholesterol: Could lead to inflammation and dangerous blood clots over time

Severe chest pain: Chest pain may become frequent overtime, and have a negative impact on daily activities

Inactive white blood cells: This could reduce immunity overtime, increasing the possibility of developing a fatal infection

Appendix 18

Example of methods communicating differences to present information about treatment A (Triptyte) in Experiment 3

Liver failure after 1 year

Compared to the no-treatment group (placebo group), 61 more people out of 1000 would develop liver failure when taking Triptyte after 1 year.

1. If 1000 people took *Triptyte* for 1 year, how many people will develop liver failure?
2. Compared to the placebo group, approximately how many **MORE** people taking *Triptyte* will develop liver failure after 1 year?

☐ 50 ☐ 250 ☐ 350 ☐ 550

Liver failure after 2 years

Compared to the no-treatment group (placebo group), 148 more people out of 1000 would develop liver failure when taking Triptyte after 2 years.

1. If 1000 people took *Triptyte* for 2 years, how many people will develop liver failure?
2. Compared to the placebo group, approximately how many **MORE** people taking *Triptyte* will develop liver failure after 2 years?

☐ 150 ☐ 450 ☐ 650 ☐ 750

Liver failure after 5 years

Compared to the no-treatment group (placebo group), 231 more people out of 1000 would develop liver failure when taking Triptyte after 5 years.

Appendix 18 continued

1. If 1000 people took *Triptyte* for 5 years, how many people will develop liver failure?
2. Compared to the placebo group, approximately how many **MORE** people taking *Triptyte* will develop liver failure after 5 years?

☐ 200 ☐ 450 ☐ 650 ☐ 750

Joint pain after 1 year

In a clinical trial, 201 out of 1000 people on Triptyte developed joint pains, compared to 95 out of 1000 people who did not take the treatment (placebo group).

Compared to the no-treatment group (placebo group), about 9 people would need to take Triptyte for 1 person to develop joint pain after 1 year

1. If 1000 people took *Triptyte* for 1 year, how many people will develop joint pains?
2. Compared to the placebo group, approximately how many **MORE** people taking *Triptyte* will develop joint pains after 1 year?

☐ 100 ☐ 250 ☐ 450 ☐ 600

Joint pain after 2 years

In a clinical trial, 465 out of 1000 people on Triptyte developed joint pains, compared to 150 out of 1000 people who did not take the treatment (placebo group).

Compared to the no-treatment group (placebo group), about 3 people would need to take Triptyte for 1 person to develop joint pain after 2 years

1. If 1000 people took *Triptyte* for 2 years, how many people will develop joint pains?
2. Compared to the placebo group, approximately how many **MORE** people taking *Triptyte* will develop joint pains after 2 years?

☐ 150 ☐ 300 ☐ 500 ☐ 750

Appendix 18 continued***Joint pain after 5 years***

In a clinical trial, 588 out of 1000 people on Triptyte developed joint pains, compared to 314 out of 1000 people who did not take the treatment (placebo group).

Compared to the no-treatment group (placebo group), about 4 people would need to take Triptyte for 1 person to develop joint pain after 5 years

1. If 1000 people took *Triptyte* for 5 years, how many people will develop joint pains?
2. Compared to the placebo group, approximately how many **MORE** people taking *Triptyte* will develop joint pains after 5 years?

☐ 100 ☐ 250 ☐ 800 ☐ 950

Remain free of severe chest pain after 1 year

Compared to the no-treatment group (placebo group), about 4 people would need to take Triptyte for 1 person to remain free of severe chest pain after 1 year

1. 1000 people took Triptyte for 1 year, how many people will remain free of chest pains?
2. Compared to the placebo group, approximately how many **MORE** people taking Triptyte will remain free of severe chest pain after 1 year?

☐ 50 ☐ 250 ☐ 500 ☐ 750

Remain free of severe chest pain after 2 years

Compared to the no-treatment group (placebo group), about 3 people would need to take Triptyte for 1 person to remain free of severe chest pain after 2 years

Appendix 18 continued

1. If 1000 people took *Triptyte* for 2 years, how many people will remain free of chest pains?
2. Compared to the placebo group, approximately how many **MORE** people taking *Triptyte* will remain free of severe chest pain after 2 years?

☐ 100 ☐ 300 ☐ 550 ☐ 600

Remain free of severe chest pain after 5 years

Compared to the no-treatment group (placebo group), about 3 people would need to take *Triptyte* for 1 person to remain free of severe chest pain after 5 years

1. If 1000 people took *Triptyte* for 5 years, how many people will remain free of chest pains?
2. Compared to the placebo group, approximately how many more people taking *Triptyte* will remain free of severe chest pain after 5 years?

☐ 20 ☐ 300 ☐ 600 ☐ 850

Appendix 19

Table Williams squares for all 24 sequences used in the crossover RCT design in Experiment 4

Williams Square	Period 1	Period 2	Period 3	Period 4
1	A	B	C	D
1	B	D	A	C
1	C	A	D	B
1	D	C	B	A
2	A	C	B	D
2	B	A	D	C
2	C	D	A	B
2	D	B	C	A
3	A	D	C	B
3	B	C	D	A
3	C	A	B	D
3	D	B	A	C
4	A	B	D	C
4	B	C	A	D
4	C	D	B	A
4	D	A	C	B
5	A	C	D	B
5	B	D	C	A
5	C	B	A	D
5	D	A	B	C
6	A	D	B	C
6	B	A	C	D
6	C	B	D	A
6	D	C	A	B

A = Standard consultation verbal; B= Standard consultation written; C = BRIMMS verbal; D = BRIMMS written; RCT = Randomised controlled trial

Appendix 20

Hypothetical disease presented to patients in Experiment 4

Trylan's Disease



The following information is about a fake medical disease, Trylan's Disease, which is a chronic medical condition (a progressive condition) and can lead to complications in the pancreas and kidneys

Without any treatment and as the disease progresses, a patient may experience the following symptoms:

- Type 2 diabetes: With progression of the disease, people are likely to develop Diabetes which would require daily management with medications
- Kidney stones: People may frequently experience kidney stones over time, which may require surgery. Regular monitoring will be required to detect kidney stones
- Kidney failure: In the very severe form of the disease, people may experience kidney failure and require dialysis. Regular monitoring and scans during the condition will be used to detect kidney failure

Appendix 21

BRIMMS protocol presented to patients for one hypothetical treatment in Experiment 4: aural condition (all information, except graphs, read aloud) and written condition (all information read aloud and given to patients in written form)

Benefits of taking Redicin

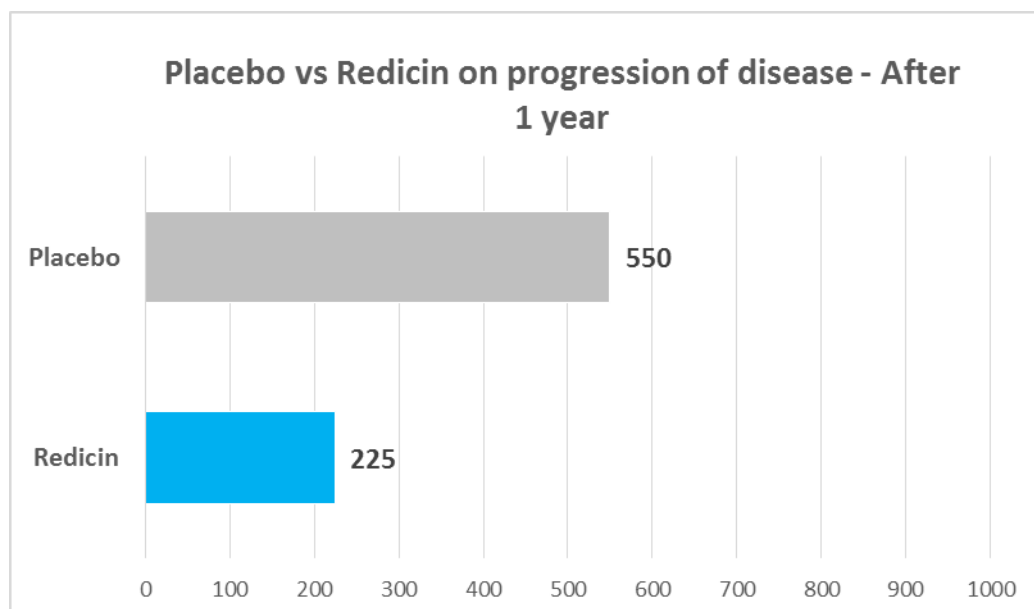
In a clinical trial, 1000 patients were given Redicin and 1000 patients were given a placebo, or a fake pill.

This was to show the benefits of taking the medication on progression of disease.

After 1 year of taking the placebo, the disease continues to progress rapidly for 550 people out of 1000

After 1 year of taking Redicin, the disease continues to progress rapidly for 225 people out of 1000

So after taking Redicin for 1 year, disease progression slowed down for 325 people

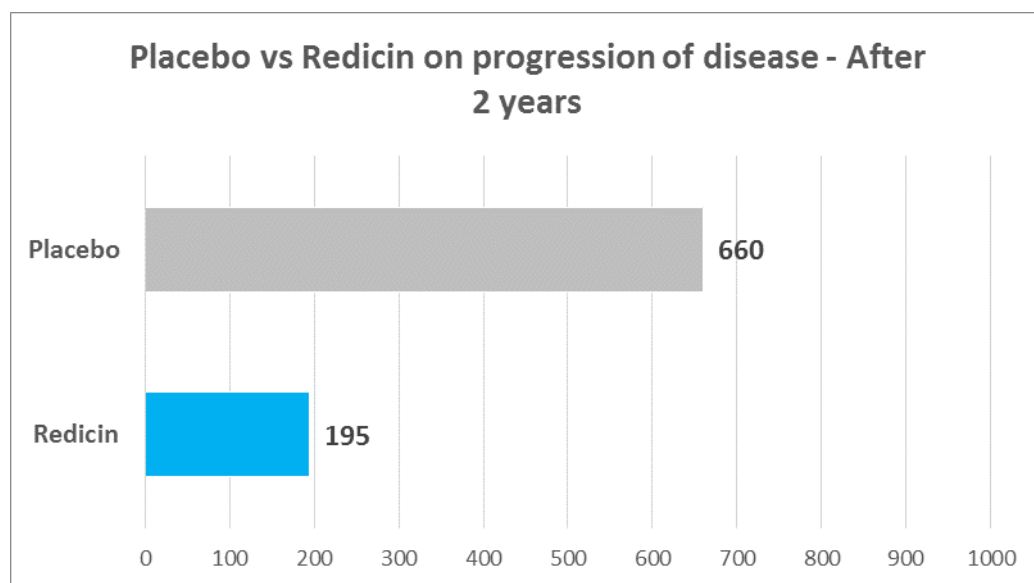


Appendix 21 continued

After 2 years of taking the placebo, the disease continues to progress rapidly for 660 people out of 1000

After 2 years of taking Redicin, the disease continues to progress rapidly for 195 people out of 1000

So after taking Redicin for 2 years, disease progression slowed down for 465 people

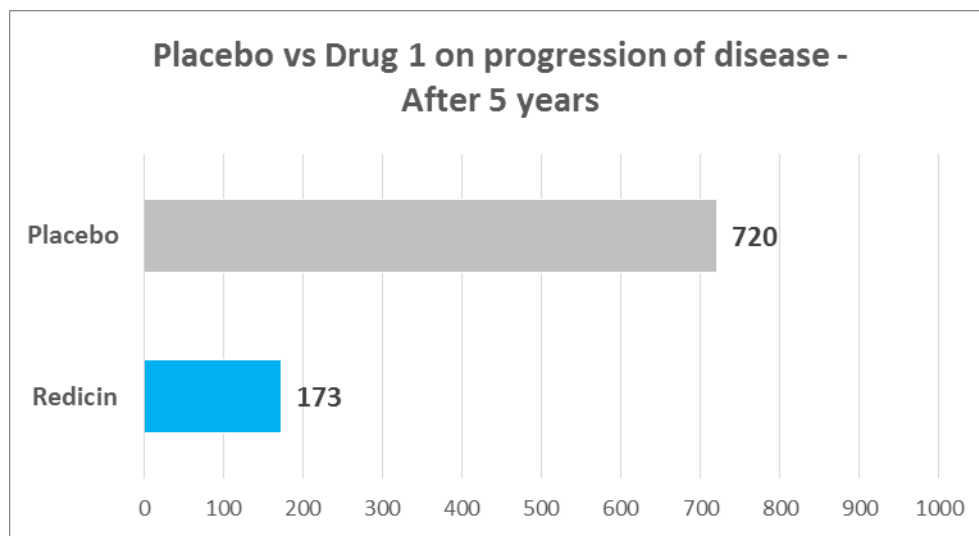


After 5 years of taking the placebo, the disease continues to progress rapidly for 720 people out of 1000

After 5 years of taking Redicin, the disease continues to progress rapidly for 173 people out of 1000

So after taking Redicin for 5 years, disease progression slowed down for 567 people

Appendix 21 continued

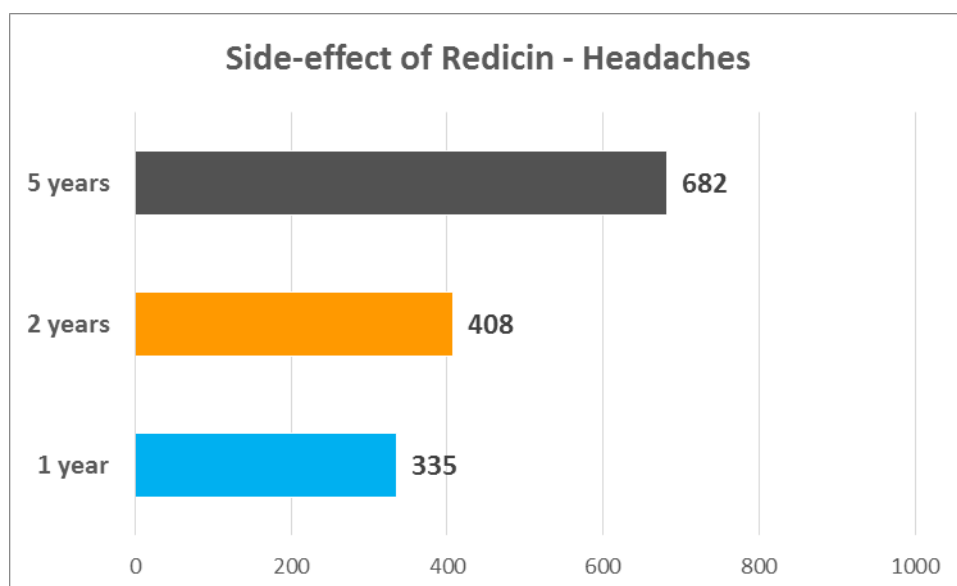
*Side-effect of taking Redicin*

A side-effect of taking Redicin is headaches

After 1 year of taking Redicin, 335 people out of 1000 could experience headaches

After 2 years of taking Redicin, 408 people out of 1000 could experience headaches

After 5 years of taking Redicin, 682 people out of 1000 could experience headaches



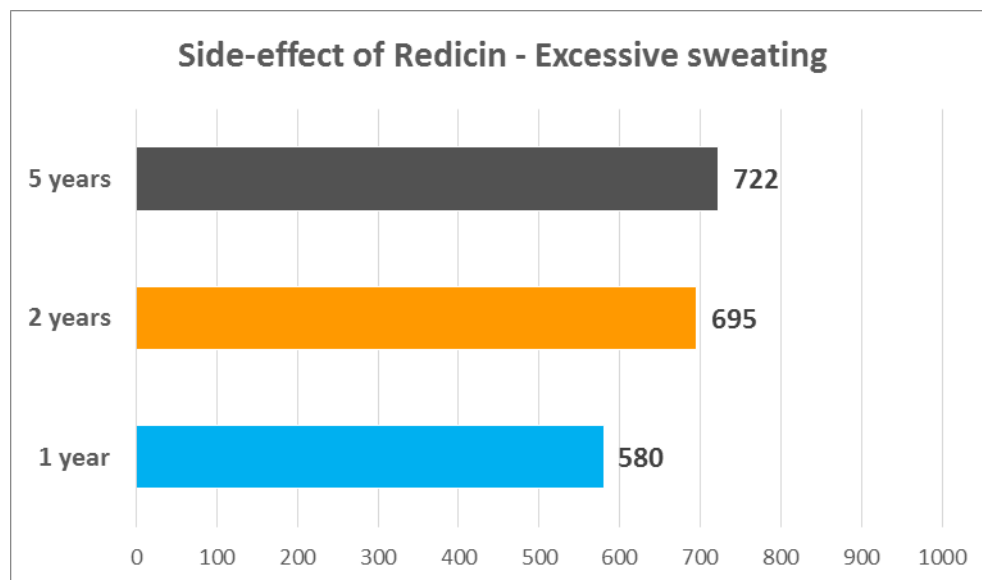
Appendix 21 continued***Side-effect of taking Redicin***

Another side-effect of taking Redicin is excessive sweating.

After 1 year of taking Redicin, 580 people out of 1000 could experience excessive sweating

After 2 years of taking Redicin, 695 people out of 1000 could experience excessive sweating

After 5 years of taking Redicin, 722 people out of 1000 could experience excessive sweating



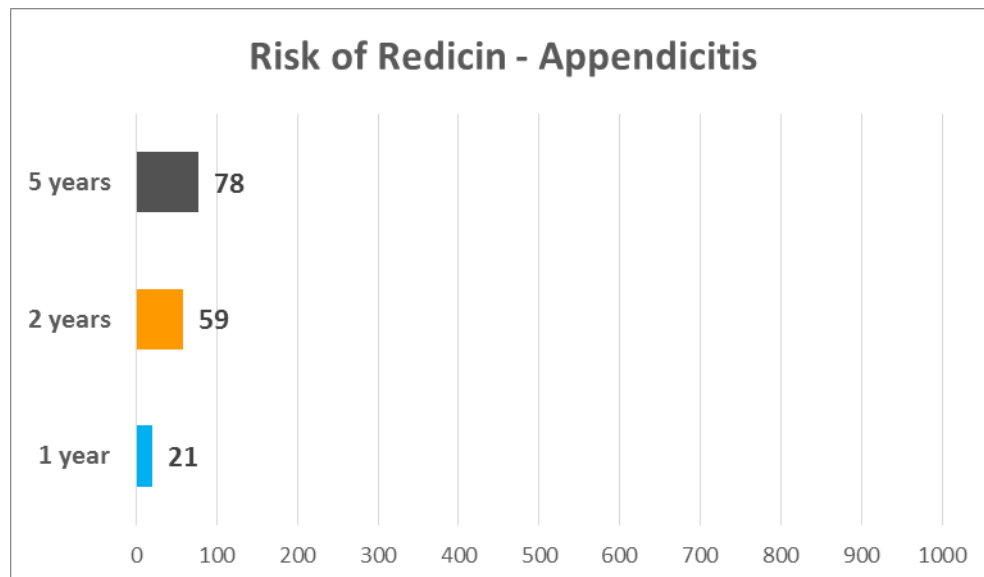
Appendix 21 continued***Risks of taking Redicin***

A risk of taking Redicin is appendicitis

After 1 year of taking Redicin, 21 people out of 1000 could develop appendicitis

After 2 years of taking Redicin, 59 people out of 1000 could develop appendicitis

After 5 years of taking Redicin, 78 people out of 1000 could develop appendicitis



Appendix 22

Standard consultation to presented to patients for one hypothetical treatment in
Experiment 4: Aural condition (all information read aloud) and written condition (all
information read aloud and given to patients to in written form)

Benefits of taking Redicin

In a clinical trial, some patients were given Redicin and some were given a placebo, a
fake pill.

This was done to show the benefits of taking the medication on how this slows the
progression of disease.

After 1 year of taking Redicin, the progression of disease slowed down by 59% compared
to patients taking a placebo

After 2 years of taking Redicin, the progression of disease slowed down by 70%
compared to patients taking a placebo

After 5 years of taking Redicin, the progression of disease slowed down by 76%
compared to patients taking a placebo

Side-effect of taking Redicin

A side-effect of taking Redicin is headaches

This side-effect is very common, as it effects over 1 in 100 people after 1 year, 2 years
and 5 years of taking Redicin

Side-effect of taking Redicin

Another side-effect of taking Redicin is excessive sweating

This side-effect is very common, as it effects over 1 in 100 people after 1 year, 2 years
and 5 years of taking Redicin

Appendix 22 continued

Risks of taking Redicin

A risk of taking Redicin is appendicitis

After 1 year of taking Redicin, more than 1 in 100 people could develop appendicitis

After 2 years of taking Redicin, more than 1 in 100 people could develop appendicitis

After 5 years of taking Redicin, more than 1 in 100 people could develop appendicitis

Appendix 23

Information and consent form for Experiment 4



Participant information Sheet:

Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS)

Randomised Controlled Trial

We would like to invite you to take part in our research study. This research study is being conducted as part of a PhD project at Royal Holloway, University of London. Before you decide to take part we would like you to understand why the research is being done and what it would involve for you. Please take the time to read the following information carefully and discuss it with others if you wish. One of our team will go through the information sheet with you and answer any questions you have, so ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?

We are conducting this study to compare how different ways of presenting risk and benefit information about drugs affect understanding and recall. This will help us identify how this information can be presented in the most effective way.

Why have I been invited to take part?

People who have been diagnosed with Multiple Sclerosis and are currently taking disease-modifying drugs (DMDs) have been invited to take part. We are hoping to recruit about 200 patients in total in the next 3 years.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide not to, it will in no way affect the care you receive. If you decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form. Even if you do agree to participate you may withdraw at any time without giving a reason.

Appendix 23 continued**What will I have to do?**

Sometimes, we don't know how best to present risk and benefit information of medications to people with MS. In this study, we will present people with different methods of presenting information of pretend drugs. You will then be asked about the data that was shown to you and we will see how well you remember this data. You will also be asked to complete a questionnaire that looks at your decisions based on this data.

The results will then be compared to see which method of presenting information is most easily understood and remembered. To try to make sure the people do not all see the same methods of information in the same order, you will be presented different methods by chance (randomly) and you will have an equal chance of receiving any order.

Before the study task, you may also be required to fill in some questionnaires to find out some background information about you, and your clinical history. You will also be requested to complete a few questionnaires and tasks, which will inform us about your mood, fatigue, as well as memory and concentration.

The whole session may take around 2 to 3 hours. However, breaks will be given throughout the study and if at any point you feel uncomfortable or tired, you may also ask for additional breaks. You will receive further information throughout the study but if you require additional help or clarification you may let us know at any time. If you feel uncomfortable at any point in the study, you can stop at any time and you may also wish to contact your MS Nurse or Doctor to discuss this.

What are the possible benefits of taking part?

We cannot promise that taking part in this study will help you, but the information we get from this study will help improve the risk and benefit information that people with Multiple Sclerosis receive about medications.

Appendix 23 continued



Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research study will be kept strictly confidential and will only be viewed by authorised researchers in the research team. All data that is used beyond the research institution will be coded and anonymised, so you will not be identified.

What will happen to the results of the study?

If the results of the study are published, participants will be kept anonymous and will not be identified in any reports or publication.

Any direct quotations used from the study will be kept completely anonymous.

Who is organising and funding the research?

The research is being funded by Royal Holloway, University of London and a pharmaceutical company named Biogen Idec Limited.

Who has reviewed the study?

This research study is part of the NHS and has been looked at by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by South Central Oxford C Research Ethics Committee.

The research has also been approved by the Ethics Committee at Royal Holloway, University of London.

Contact details

If you have any questions about this study or would like more information about this research project, please contact:

Miss Gurpreet Reen - Royal Holloway, University of London

Email: gurpreet.reen.2014@live.rhul.ac.uk

Telephone: 0787 845 1844

Appendix 23 continued



Consent form

Benefit and Risk Information for Medication in Multiple Sclerosis (BRIMMS)

Randomised Controlled Trial

1. I confirm that I have read and understood the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

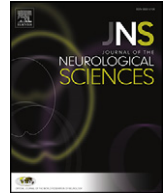
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected. ☐

3. I agree to take part in the above study. ☐

Name of Participant

Date

Signature



Review Article

Multiple sclerosis patients' understanding and preferences for risks and benefits of disease-modifying drugs: A systematic review

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Shared decision-making

ABSTRACT

Background: Multiple sclerosis (MS) patients are faced with complex risk-benefit profiles of disease-modifying drugs (DMDs) when making treatment decisions. For effective shared decision-making, MS patients should understand the risks and benefits of DMDs and make treatment decisions based on personal preferences.

Methods: This is an inclusive systematic review to primarily assess current understanding of MS patients for information about DMDs provided during the standard healthcare system. The secondary aim assesses MS patients' preferences for specific risks and benefits of treatments. A systematic search was conducted using PubMed, Embase and Google Scholar. A total of 22 studies were reviewed across both aims. Relevant quantitative and qualitative data was extracted by two authors. A narrative synthesis was conducted due to heterogeneity of research findings.

Results: There was a trend for DMD risks to be generally underestimated and DMD benefits to be generally overestimated by MS patients. Treatments that could potentially offer substantial symptom improvement, delay in disease progression, or reduction in relapses were preferred even at the expense of higher risks.

Conclusions: Many patients' experience of information during the standard healthcare system does not provide satisfactory understanding of the risks and benefits of DMDs. Effective ways to communicate risk and benefit DMD information when making shared treatment decisions needs to be identified. Patient preferences of DMD risks and benefits should also be taken into account.

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1. Introduction

Multiple sclerosis (MS) is a chronic immunological disease of the central nervous system which progresses at different rates between individuals [1,2]. Disease-modifying drugs (DMDs) are treatments which can delay the progression of MS, but often present complex profiles of risks and benefits [3]. DMDs typically provided at the earlier stages of MS are selected for their long-term safety profiles and minimal monitoring requirements, and are generally referred to as first-line treatments [4]. The efficacy of these therapies is modest [5]. More aggressive DMDs may be considered when initial therapies are not effective. These DMDs generally offer superior efficacy but also higher probabilities of adverse effects, which can range from flu-like symptoms to fatal conditions such as leukaemia or progressive multifocal leukoencephalopathy (PML) [3,6–9]. MS patients are thus faced with complex risk-benefit profiles when deciding on the best course of treatment.

A shared decision-making approach is particularly suited for a chronic condition such as MS, where there is great complexity and uncertainty about suitable treatments for an individual [10,11]. This approach is defined as the shared and proactive exchange of information between health professionals and patients, when making treatment decisions during consultations [12–14]. Effective shared decision-making in MS should improve patients' understanding of the risks and benefits of DMDs and allow patients to make treatment decisions in accordance with their personal values, which will likely improve patient engagement in the decision-making process [15,16].

Evidence-based information about DMDs should be effectively communicated during consultations based on the shared decision-making approach, since many MS patients seek autonomy during treatment decisions [17,18]. Autonomous patients desire accurate information about treatments, which includes current research findings about DMD risks and benefits [19,20]. If accurate information is not provided during consultations, it is likely that autonomous patients will seek information beyond the health care system that may be inaccurate or outdated. The benefits of providing clear and accurate treatment information to patients is also evident beyond initial treatment decision. One such benefit is improvement in treatment adherence, as patients with accurate understanding of treatment risk-benefit profiles are less likely to discontinue treatment due to unrealistic optimistic expectations [21,22]. Hence, it is important to determine whether MS patients sufficiently understand the complex risk-benefit profiles of DMDs when information is provided during the standard healthcare system.

It is also important to elicit patient values and preferences in order for shared decision-making to work effectively [16]. Patient preference in the shared decision-making context is generally defined as patient's choice of treatment based on available treatment options [14,23]. Preference for certain risks and benefits that treatments offer may be a sensitive predictor of patient's preferred choice of treatment. For instance, patients are likely to choose a treatment compatible with the level of risks they are willing to take [24,25] and may be more likely to forgo the benefits of long-term survival for the benefits of an improved quality of life [26]. In a recent review, MS patients' perception of treatment risks was also found to greatly impact patients' treatment decisions with their neurologists during the shared decision-making process [27]. For this reason, it is important to identify the extent to which patient preferences for both the risks and benefits that DMDs typically offer can influence MS patients' treatment decision.

To the best of our knowledge, the present systematic review is the first to gather evidence on MS patients' understanding and preferences

for risks and benefits of treatments. The primary aim will evaluate MS patients' understanding of risk and benefit information for DMDs acquired during their journey through standard healthcare systems, preceding any interventions or decision aids that may be provided beyond regular consultations. The secondary aim will identify MS patients' preferences for treatment risks and benefits across studies, and assess whether these preferences can have an impact on patient's treatment decisions.

2. Method

2.1. Systematic literature search

The systematic literature search was conducted in February 2016 through PubMed, Embase and Google Scholar using specific search terms for both study aims (see Table 1). After removing duplicate entries, a total of 889 records were identified (see Fig. 1).

Studies were eligible for inclusion if they were: in English, with human adults and of any study design. Studies with patients of any MS disease subtype were included. No date restriction was applied. For both aims, studies were included if they had some evaluation of disease-modifying drugs and when the evaluations focused on patients with MS.

Studies were excluded if they discussed medications for MS symptom management or complementary medicines. Studies with evaluation of patients' understanding of disease-modifying drugs post educational intervention was not included. However, baseline measures prior to any educational intervention were eligible for inclusion in the present review. Studies that assessed MS patients' understanding for other areas in MS, including diagnosis and prognosis, were excluded. Studies focusing only on patients' adherence to DMDs were also excluded.

Following screening of titles and abstracts, 835 records were excluded. Full texts were subsequently accessed. Studies that were considered relevant from screening references were also identified. Thus, data was extracted for a total of 58 full-texts, and studies were included into the final review if inclusion and exclusion criteria were met (see Fig. 1).

2.2. Data extraction

Data extraction was carried out by one reviewer (GR) using data extraction forms specifically designed for the current review, and was verified by another (DL). Any discrepancies were resolved by discussion. After extraction of full texts, a total of 22 studies were included into

Table 1
Search terms for systematic review: primary aim and secondary aim.

Search terms for systematic review
(Multiple AND Sclerosis)
AND
(patients OR people OR persons OR patient)
AND
(risk OR benefit OR side effect)
AND
(treatment OR medication OR therapy OR medicine OR medical OR therapies OR therapeutics OR Pharmaceutical preparations)
AND
(perception OR understanding OR comprehension OR awareness OR knowledge OR information OR communication OR preference OR decision-making)

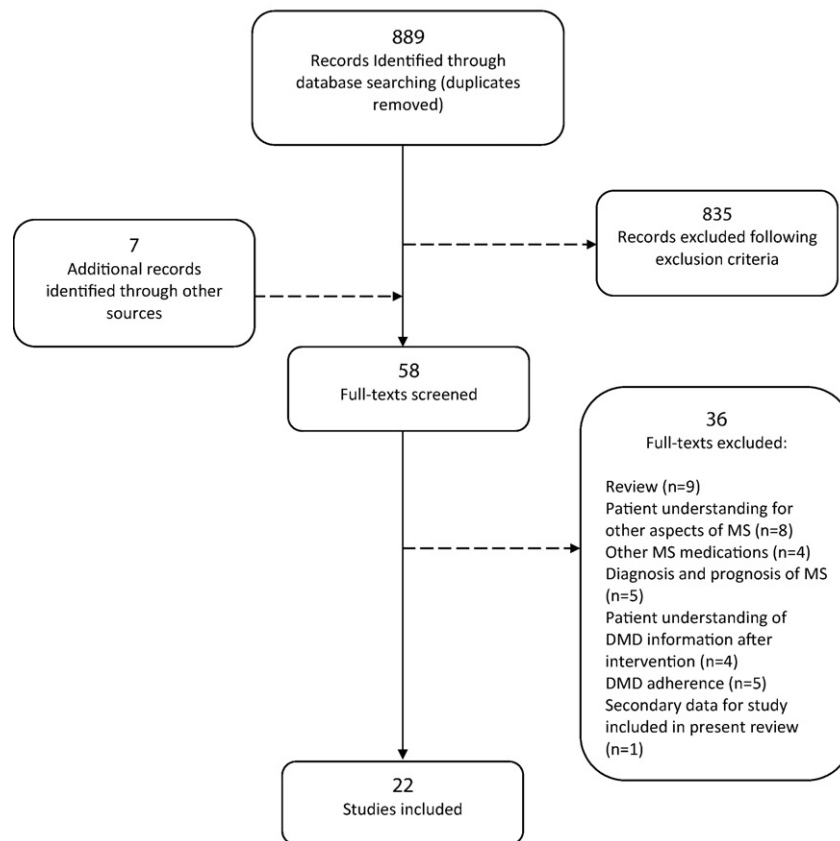


Fig. 1. Flow diagram for included studies: primary aim and secondary aim.

the final review across both study aims. One study had relevant findings for both the primary aim and secondary aim. Thus, 14 studies were included into the primary aim and 9 studies were included into the secondary aim.

Baseline characteristics of MS patients were extracted from all 22 studies, which covered age, the type of MS and current DMD status. Since very few studies exclusively assessed understanding or preferences of treatment risks and benefits in MS, studies with any evaluation of either aims were retained.

For the primary aim, any data available on understanding of treatment risks or benefits, or understanding of the treatment overall, was retained. Only understanding of information about real DMDs was incorporated into this aim. This information sometimes existed as baseline measures in intervention studies. Both self-report and objective

measures were included for review, in addition to themes from qualitative studies.

For the secondary aim, patients' preferences for treatment risks only, treatment benefits only and a combined trade-off between treatment risks and benefits were considered. Preferences for treatment risks and benefits were defined as patients' attitudes towards risks and benefits, the levels of risks and benefits MS patients were willing to accept, or MS patients' perception of their current DMD. Preferences for risks and benefits of both real DMDs and hypothetical treatment scenarios were included in this aim, providing that hypothetical risk-benefit scenarios were relevant to MS. Similar to the primary aim, information from self-report and objective measures were discussed.

Relevant data was obtained from numerical information in texts, tables, graphs, and relevant statistical analysis. For qualitative studies,

Table 2

Quality assessment of studies investigating MS patients' understanding of DMD risks and benefits: primary aim.

First author (year)	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropout	Overall quality rating
Mohr (1996)	Moderate	Moderate	–	Moderate	Strong	Strong	Strong
Heesen (2003)	Weak	Weak	–	Moderate	Weak	Weak	Weak
Heesen (2004)	Moderate	Weak	–	Moderate	Strong	Moderate	Moderate
Vlahiotis (2010)	Weak	Weak	–	Moderate	Moderate	Weak	Weak
Visser (2011)	Weak	Moderate	–	Moderate	Weak	Moderate	Weak
de Seze (2012)	Weak	Weak	–	Moderate	Strong	Weak	Weak
Hofmann (2012)	Weak	Moderate	–	Moderate	Weak	Weak	Weak
Kopke (2014)	Strong	Strong	Strong	Strong	Strong	Strong	Strong
Syed (2014)	Weak	Moderate	–	Moderate	Moderate	Weak	Weak
Abolfazli (2014)	Weak	Weak	–	Moderate	Weak	Strong	Weak
Zimmer (2015)	Moderate	Moderate	–	Moderate	Moderate	Strong	Moderate

Overall quality rating: strong = no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Table 3

Quality assessment of qualitative studies investigating MS patients' understanding of DMD risks and benefits: primary aim.

First author (year)	Clear aims	Appropriate methodology	Appropriate design	Appropriate recruitment strategy	Data collection method	Researcher and participant relationship considered	Ethical issues considered	Rigorous data analysis	Statement of findings	Is the research valuable?
Miller (2001)	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes
Miller (2006)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Miller (2012)	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes

Quality assessed using the Critical Appraisal Skills Programme tool (CASP); all categories marked as either yes, no or can't tell/unclear.

relevant themes were extracted and discussed. Medication names are given as reported in each study. Due to the heterogeneity of the studies in the present review, a narrative synthesis was conducted.

2.3. Quality assessment

All studies in this review were examined independently for quality by two reviewers (GR and DL) using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies [28]. This particular tool was chosen because it is often used to evaluate different types of quantitative studies in the health care setting [29], it has high inter-rater reliability [29] and is considered ideal for use in systematic reviews [30]. As per the tool, the final quality rating was derived from the rating of 6 measures (see Tables 2 and 4).

The Critical Appraisal Skills Programme (CASP) tool was used to appraise the quality of qualitative studies in this review (see Table 3). This tool was chosen as it has often been recommended for reviewers [31] and was previously used in other systematic reviews [32].

3. Results

3.1. Results: primary aim

3.1.1. Patient and study characteristics

A total of 14 studies were included in the primary aim (see Tables 5 and 6). With the exception of three qualitative studies [33–35], the studies mostly consisted of surveys and questionnaires. Data from some studies was derived from baseline measures of randomized-controlled trials [36–38]. Two quantitative studies were found to have the strongest quality rating [36,38].

Across the 14 studies, a total 8032 patients were included with a range of MS disease subtypes, which comprised: 27 (0.3%) patients with clinically isolated syndrome (CIS), 2532 (31.5%) relapsing-remitting MS (RRMS) patients, 349 (4.3%) primary progressive MS (PPMS) patients and 870 (10.8%) secondary progressive MS (SPMS) patients. Of the remaining, 251 (3.1%) patients were reported as having benign MS, with unclear or unreported MS disease subtype for all other MS patients (49.8%). The mean age of patients was 42 (range: 34–50). The mean value excludes MS patients in studies that only stated the median

values of age [39], the range of ages [34,35] and those studies that did not specify age of MS patients [36,40].

Of the studies which recorded patient's current DMD, the majority of patients were taking first-line treatments, including interferons in seven studies [34,36,38,40–43] and glatiramer acetate in four studies [35,38,40,41]. MS patients taking aggressive medications were also recorded, including Natalizumab [33], Fingolimod [37] and Mitoxantrone [40,44]. Eight studies focused primarily on MS patients taking a single DMD [33–37,42–44].

3.1.2. Study outcomes

3.1.2.1. Understanding of overall treatment information. MS patients' understanding of overall DMD information during the routine healthcare system was assessed using questionnaires and surveys by seven studies.

Self-report measures in one study indicated that 44% of MS patients considered themselves extremely well-informed about their current DMD [42]. Using a visual analogue scale in another study, just under 20% of patients reported being fully informed about current DMDs [37]. Using retrospective surveys, 28% of patients reported being well-informed about DMDs at time of diagnosis, with just over 50% patients stating that they did not receive any information about DMDs at diagnosis [45]. On the other hand, between 75% to 84% of MS patients reported being partly or totally informed about current DMDs [39,41], and 85% of MS patients felt they were aware about other DMD treatment options based on one question from a 12-item questionnaire [40]. Of those patients who felt informed about DMDs, 71% of MS patients felt the information received was of a sufficient standard [45].

Objective measurements were used by two studies within the present review to establish MS patients' understanding of overall treatment information. Abolfazli and colleagues [43] administered a 25-item questionnaire to MS patients, nine questions of which assessed understanding of the first-line treatments in general, and three questions each focused on understanding of the five specific DMDs that fell within this category. Only 30% of MS patients were able to correctly answer seven of the nine questions that assessed understanding of the drugs generally, with the remaining two questions answered correctly by just over 60% of MS patients. The authors concluded that understanding of overall information about first-line DMDs was low for the assessed

Table 4

Quality assessment of studies investigating MS patients' preferences for treatment risks and benefits: secondary aim.

First author (year)	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropout	Overall quality rating
Prosser (2002)	Moderate	Weak	–	Moderate	Strong	Strong	Moderate
Kasper (2008)	Strong	Strong	Strong	Strong	Moderate	Strong	Strong
Johnson (2009)	Weak	Weak	–	Moderate	Strong	Strong	Weak
Tur (2013)	Moderate	Moderate	Moderate	Weak	Moderate	Strong	Moderate
Abolfazli (2014)	Weak	Weak	–	Moderate	Weak	Strong	Weak
Wilson (2014)	Moderate	Weak	–	Moderate	Moderate	Moderate	Moderate
Bruce (2015)	Moderate	Weak	–	Moderate	Moderate	Weak	Weak
Fox (2015)	Weak	Weak	–	Moderate	Moderate	Weak	Weak
Wilson (2015)	Moderate	Weak	–	Moderate	Weak	Strong	Weak

Overall quality rating: strong = no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Table 5

Patient and study characteristics, and results of quantitative studies investigating MS patients' understanding of DMD risks and benefits: primary aim.

First author (year)	Quality rating	Study design and methodology	Recruitment location	Sample size	Age (mean)	Type of MS (n)	DMD	Real/faux information	Self-report or objective measure	Outcome measure(s)	Results
Mohr (1996)	Moderate	Questionnaire: baseline data from a pre-post intervention study	Outpatient clinics	99	–	Not specified	Interferon beta-1b	Real	Objective	DMD benefit understanding: survey items from BSQ	Relapse rate: Expected <10% reduction ('overly pessimistic group') = 4% patients Expected 10–30% reduction ('accurate group') = 39% patients Expected >50% reduction ('overly optimistic group') = 57% patients Disease progression: Expected no change = 40% patients Expected slower progression = 26% patients Expected some restoration of function = 29% patients Expected return to normal function = 4% patients
Heesen (2003)	Weak	Postal questionnaire: observational study	MS patient organisation	434	Women = 44; men = 43	Not specified	DMD not specified	Real	Self-report	Understanding of overall DMD information: 3 questions from 13-item questionnaire	52% of patients not informed at time of diagnosis; 28% of patients informed after several months of diagnosis; 71% of patients received sufficient information 34% answers correct
Heesen (2004)	Weak	Postal questionnaire: observational study	MS outpatient clinic	169	44	RRMS (75); PPMS (75); unclear (19)	DMD not specified	Real	Objective	DMD risk understanding: 10 questions about DMD risks out maximum 19	63% of perceived knowledge
Vlahiotis (2010)	Weak	Postal survey: observational study	American health insurance database	2022	–	PPMS (78); RRMS (1493); SPMS (213) Other (29); unknown (209)	Interferon-beta 1a IM; interferon beta 1a SC; interferon-beta 1b; glatiramer acetate; Mitoxantrone	Real	Self-report	DMD benefit understanding: survey questions	DMD helps MS: Females = 79%; males = 72%
									Self-report	Understanding of overall DMD information: survey questions	Awareness of other treatment options: Females = 85%; males = 80%
Visser (2011)	Weak	Postal survey: observational study	Hospitals; MS patient organisation	1371	Benign MS & RRMS = 47 ¹ ; SPMS = 51 ¹ ; PPMS = 52 ¹	Benign MS (251); RRMS (525); PPMS (120); SPMS (399); unknown (76)	DMD not specified	Real	Self-report	Understanding of overall DMD information: 1 item from 72-item questionnaire; enough treatment information received?	'Taking first DMD' group: 81% patients agree; 9% patients neutral; 10% patients disagree 'Changed DMD' group: 84% patients agree; 7% patients neutral; 9% patients disagree

(continued on next page)

Table 5 (continued)

First author (year)	Quality rating	Study design and methodology	Recruitment location	Sample size	Age (mean)	Type of MS (n)	DMD	Real/faux information	Self-report or objective measure	Outcome measure(s)	Results
de Seze (2012)	Weak	Postal questionnaire: Observational study	Hospitals and community practise	202	41	RRMS (202)	Interferon-beta 1a; interferon-beta 1b; glatiramer acetate	Real	Self-report Self-report	Understanding of overall DMD information: 'well informed about treatment?' DMD benefit understanding	'Stopped DMD' group: 74% patients agree; 15% patients neutral; 11% patients disagree Totally agree = 35%; partly agree = 40%; partly disagree = 14%; totally disagree = 5%; no opinion = 2% Reduced relapse frequency with current DMD: Totally agree = 50%; partly agree = 40%; partly disagree = 6%; totally disagree = 2%; no opinion = 3% Delay in treatment progression with current DMD: Totally agree = 36%; partly agree = 50%; partly disagree = 9%; totally disagree = 2%; no opinion = 5% Optimistic about MS due to DMD: Totally agree = 28%; partly agree = 45%; partly disagree = 17%; totally disagree = 7%; no opinion = 3% Leukaemia: Accurate risk choice = 40% patients Underestimated risk = 58% patients Cardiotoxicity: Accurate risk choice = 16% patients Underestimated risk = 82% patients IG at baseline (n-93) 35% patients with 'good risk knowledge'
Hofmann (2012)	Moderate	Postal questionnaire: Retrospective cohort study	Database of hospitals and private clinics	575	50	RRMS (49); PPMS (76); SPMS (258); other (4); unknown (188)	Mitoxantrone	Real	Objective	DMD risk understanding: risk choice from 4 options about Mitoxantrone side-effects	Leukaemia: Accurate risk choice = 40% patients Underestimated risk = 58% patients Cardiotoxicity: Accurate risk choice = 16% patients Underestimated risk = 82% patients IG at baseline (n-93) 35% patients with 'good risk knowledge'
Köpke (2014)	Strong	Telephone and postal questionnaire: baseline data from double-blind RCT	MS outpatient clinics	192	37	CIS (27); RRMS (133); unclear (32)	Interferon-beta; glatiramer acetate	Real	Objective	DMD risk understanding: 'good risk knowledge' defined as minimum 12 answers from possible 19	

Syed (2014)	Weak	Structured questionnaire: baseline data from longitudinal study	Home support service	2390	42	Not specified	Interferon-beta 1a	Real	Self-report	Understanding of overall DMD information: 3 items from survey	CG at baseline (n = 99): 23% patients with 'good risk knowledge' 44% of patients felt extremely well informed (n = 1265)
Abolfazli (2014)	Weak	Postal questionnaire: Observational study	MS patient organisation	425	34.3	Not specified	Interferons	Real	Objective	Understanding of overall DMD information	Greater understanding associated with: High level of education (p = 0.0010) Delay between onset of symptoms and definite MS (p = 0.0190) Increased mobility (p = 0.220) Younger age (p = 0.030) Females (p = 0.001) Ability to self-inject (p = 0.003)
Zimmer (2015)	Moderate	Questionnaire: baseline data from pre-post intervention study	MS centre in hospital	98	41 ¹	Not specified	Fingolimod	Real	Objective	Understanding of overall DMD information: 18-item questionnaire	Median score = 6 out of 18 (IQR = 4–8)
									Self-report	Understanding of overall DMD information: VAS (0–10); perception of being informed	Greater understanding associated with: Females (p = 0.02) Patients in a relationship compared to singles (p = 0.03) Number of patients with following scores (n=97): Score < 7 = 78 Score ≥ 7 = 19

Absolute numbers reported, unless specified. Abbreviations: BSQ, Betaseron questionnaire; CG, control group; CIS, clinically isolated syndrome; DMD, disease-modifying drug; IG, intervention group; MS, Multiple Sclerosis; PML, progressive multifocal leukoencephalopathy; PPMS, primary progressive multiple sclerosis; RCT, randomized controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; VAS = visual analogue scale. 1 = median, 2 = range.

Table 6

Patient and study characteristics, and themes from qualitative studies investigating MS patients' understanding of DMD risks and benefits: primary aim.

First author (year)	Quality rating	Study design and methodology	Recruitment location	Sample size	Age (mean)	Type of MS (n)	DMD	Real/faux information	Self-report or objective measure	Outcome measure(s)	Results
Miller (2001)	–	Qualitative interviews	MS centre	15	28–55 ²	RRMS (15)	Interferon beta-1a	Real	Self-report	DMD benefit understanding: themes from qualitative analysis	Overestimating benefit of DMD: “I look at Avonex as my saviour. I probably expected a lot more from it than I was going to get, realistically” (pg. 242)
Miller (2012)	–	Qualitative interviews	MS centre; Natalizumab infusion centre	20	43	RRMS (20)	Natalizumab	Real	Self-report	DMD risk understanding: themes from qualitative analysis	Low risk perception for DMD: “I didn't feel that it was going to a big risk for me because I trust my doctors, and I don't think they really pushed it if they didn't feel confident” (pg. 41)
Miller (2006)	–	Qualitative interviews	MS clinic	20	39–64 ²	RRMS (20)	glatiramer acetate	Real	Self-report	DMD benefit understanding: themes from qualitative analysis	High risk perception for DMD: “I'm sure anybody who goes on Tysabri from the moment they make that decision...worry about PML”. (pg. 42) “I was so afraid to try Tysabri, you know, the warnings and the labels are just, they're so scary.” (pg. 42) Benefits of glatiramer acetate: “...the importance of getting on to these ABC drugs – Avonex, beta interferon and Copaxone – is to start as soon as you have symptoms” (pg. 39) “This way (injecting glatiramer acetate) I feel like I am doing something progressive to help it.” (pg. 39) “And I have researched the ingredients, and it is so natural” (pg. 40)

Absolute numbers reported, unless specified. Abbreviations: DMD, disease-modifying drug; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; RRMS, relapsing-remitting multiple sclerosis. 2 = range.

MS patients [43]. Another study also employed an objective questionnaire, which was presented to patients as part of a baseline measure before intervention [37]. MS patients in this study answered a median of six questions correctly about overall understanding of their current DMD from a maximum score of 18 [37]. Both studies also analysed factors which were associated with greater understanding by MS patients for overall information about DMDs. A common significant patient factor associated with better understanding across both studies was gender, since females displayed greater understanding of overall information about first-line DMDs [43] and the more aggressive treatment Fingolimod [37]. Greater understanding of overall DMD information was also related to: a high level of education [43], the delay between onset of symptoms and diagnosis of MS [43], increased mobility [43], younger age [43], ability to self-inject for some first-line treatments [43] and patients who were in a relationship as opposed to being single [37].

In summary, majority of studies which assessed MS patients' understanding of overall DMD information relied heavily on patient self-reports. Although the findings varied both within and across studies, it is clear that not all patients feel sufficiently informed about DMDs during the routine healthcare system. This is also supported by objective measures, albeit in only a few studies. The factors associated with good understanding of overall DMD information were also inconsistent, with only females showing a consistent advantage across two studies.

3.1.2.2. Understanding of treatment risks. MS patients' understanding of treatment risks was evaluated by four studies in this review.

Perceived accurate understanding of the risks of unspecified DMDs was reported by 63% of MS patients in one study [18]. A qualitative study interviewing MS patients taking the aggressive treatment Natalizumab showed mixed findings for understanding of the risks associated with this treatment; patients demonstrated both high and low perceived risks [33].

Three studies used objective questionnaires to assess understanding of DMD risks, with two of these studies administering a similar adapted 19-item questionnaire designed for newly diagnosed patients [18,38]. Approximately 30% of MS patients showed ‘good risk knowledge’ for their DMD based on their scores from this questionnaire [38]. For the other study employing a similar questionnaire, MS patients were only able to answer 34% of the questions correctly on average despite perceiving their risk knowledge as good [18]. Significant correlations were also established between greater understanding of DMD risks and patients who had been recently diagnosed, had the RRMS disease subtype, and were of a younger age [18]. To note, questionnaires employed in both studies primarily measured understanding of the risks associated with MS in general, with only a portion of the questions explicitly focusing on risk understanding of DMDs. In another study employing objective methodology for the understanding of the aggressive DMD Mitoxantrone, 55% of MS patients underestimated the risk of leukaemia, and up to 82% of MS patients underestimated the risk of cardiotoxicity; both adverse risks associated with this DMD [44]. These findings were based on baseline measures of an interventional study [44].

In summary, although MS patients show mixed perception towards their understanding of DMD risks, objective measures seem to indicate that DMD risks are generally low and underestimated by MS patients during the routine healthcare system.

3.1.2.3. Understanding of treatment benefits. MS patients' understanding of the benefits associated with their treatment was evaluated by five studies in the present review.

Over 70% of MS patients taking a range of DMDs believed their current DMD could help their MS [40]. Likewise, a large number of MS patients totally or partially perceived their current medication to have strong benefits: 90% of MS patients perceived that their DMD could reduce the frequency of MS relapses, 86% of MS patients believed that

Table 7

Patient and study characteristics, and results of quantitative studies investigating MS patients' preferences for treatment risks and benefits: secondary aim.

First author (year)	Quality rating	Study design and methodology	Recruitment location	Sample size	Age (mean)	Type of MS (n)	DMD	Real/faux information	Self-report or objective measure	Outcome measure(s)	Results
Prosser (2002)	Weak	Survey: observational study	MS clinics	56	38	RRMS (56)	Interferon-beta 1a; interferon-beta 1b; glatiramer acetate	Faux	Objective	Preferences for treatment benefits: gamble question (drug with relapse-free days compared with drug offering 50% chance of immediate reduction but 50% chance of not working)	Mean = 14.6 relapse-free days
Kasper (2008)	Strong	Questionnaire: baseline data from RCT	Newspapers; websites; national self-help journal	297	43	CIS (45); RRMS (153); PPMS (31); SPMS (59); unclear (9)	DMD not specified	Real	Self-report	Preferences for treatment benefits: Likert scale	Moderately optimistic towards current DMD; IG group at baseline = 65% patients; CG group at baseline = 62% patients
Johnson (2009)	Moderate	Survey: observational study	MS patient organisation; Natalizumab clinical trial patients	651	47	Not specified	Natalizumab	Real	Objective	Preferences for treatment risk-benefit profiles: mean annual risk acceptable to patients	Mean annual risk for 'slow progression benefit' (No. of relapses in next 5 years reduced from 4 to 1; disability progression delay from 5 to 8 years) 0.31% of PML death or disability; 0.30% of death by liver failure; 0.35% of death by leukaemia Mean annual risk for 'clinically relevant benefit' (No. of relapses in next 5 years reduced from 4 to 1; disability progression delay from 3 to 5 years) 0.38% of PML death or disability; 0.39% of death by liver failure; 0.48% of death by leukaemia Mean annual risk for 'largest tested benefit' (No. of relapses in next 5 years reduced from 4 to 0; disability progression delay from 1 to 8 years) 0.74% of PML death or disability; 1.02% of death by liver failure; 1.08% of death by leukaemia
Tur (2013)	Moderate	Survey: observational study	MS centre; hospital	136	Natalizumab group = 38; other DMD group = 39	Not specified	Natalizumab; first-line DMDs	Faux	Objective	Preference for treatment risks: five risk levels for five presented therapeutic scenarios	Mean scores for level of risks accepted: Patients taking Natalizumab (n = 114): Very low risk = 8.85; low risk = 8.49; medium risk = 7.47; high risk = 4.29; very high risk = 3.01 Patients taking any other DMD (n = 22): Very low risk = 7.50; low risk = 6.32; medium risk = 4.76; high risk = 2.43; very high risk = 1.58
Abolfazli, 2014	Weak	Questionnaire: observational study	MS patient organisation	425	34.3	Not specified	Interferons	Real	Self-report	Preference for treatment benefits: 5-point Likert scale across 13 questions	Optimistic about current DMD = 20% to 90% patients

(continued on next page)

Table 7 (continued)

First author (year)	Quality rating	Study design and methodology	Recruitment location	Sample size	Age (mean)	Type of MS (n)	DMD	Real/faux information	Self-report or objective measure	Outcome measure(s)	Results
Wilson (2014)	Moderate	Questionnaire: conjoint analysis	MS clinic	289	42	RRMS (289)	Interferons; Natalizumab; glatiramer acetate; Fingolimod; Rituximab	Faux	Objective	Preference for treatment risk-benefit profiles: estimated acceptable risk for various DMD benefits	Optimistic about DMD associated with: Lack of functional problem ($p = 0.004$) No MS family history ($p = 0.029$) Knowledge of interferons ($p = 0.001$) For 1% risk of DMD severe side-effects, patient preference for treatment decreased by 5 times
									Objective	Preference for treatment risks: odds ratio	Minor side effect: Headache flu = 0.98 Mood change = 0.91 ($p < 0.001$)
									Objective	Preference for treatment benefits: odds ratio	Severe side effect: 0.05% = 0.70 ($p < 0.001$) 0.10% = 0.60 ($p < 0.001$) 1% = 0.22 ($p < 0.001$) Progression prevention: 2 years = 1 4 years = 1.36 ($p < 0.001$) 10 years = 2.46 ($p < 0.001$)
											Delay in relapse: 1 year = 1 2 years = 1.20 ($p < 0.001$) 5 years = 1.53 ($p < 0.001$)
											Symptom improvement: None = 1 Mild = 1.75 ($p < 0.001$) Substantial = 3.68 ($p < 0.001$)
Bruce, 2015	Weak	Questionnaire: probability discounting	MS Clinics	77	Adherent = 43.26; non-adherent = 45.03	RRMS	Not specified	Faux	Objective	Preferences for treatment risk-benefit profiles: Medical Decision Making Questionnaire	Chosen treatment benefit related to side-effect probability ($p < 0.001$) interaction between side effect and group (adherent and non-adherent) for treatment benefits chosen ($p < 0.001$)
Fox, 2015	Weak	Survey: observational study	North American Research Committee on Multiple Sclerosis (NARCOMS) Registry	5446	52.7	Not specified	Not specified	Faux (cure for MS) and real (Natalizumab)	Objective	Preference for treatment risk: standard gamble paradigm	Improbable side-effects predict treatment adherence = 83.1% Median risk tolerance for both scenarios = 1:10,000 Faux DMD scenario: No risk tolerance = 23% Tolerate any risk = 3.6% Faux DMD risk tolerance associated with: No disability = 1:100,000 versus wheelchair-bound = 1:1000 ($p < 0.0001$);

Wilson, 2015	Weak	Survey: conjoint analysis	MS clinic	50	42.7	RRMS	Glatiramer acetate; interferon beta; Natalizumab; Rituximab; Fingolimod; no-treatment	Faux	Objective	Preference for treatment risk	<p>Male = 1:2000 versus females = 1:50,000 ($p < 0.0001$); Patients caring for dependents = 1:100,000 versus not caring for dependents = 1: 10,000 ($p < 0.0001$); Patients taking DMD = 1:50,000 versus not taking DMD = 1:50,000 ($p = 0.002$); Patients taking Natalizumab = 1:1000 versus not taking Natalizumab = 1:50,000 ($p < 0.0001$); Patients who routinely use seatbelt = 1:50,000 versus those who do not routinely use seatbelt = 1:5000 ($p = 0.0007$)</p> <p>Natalizumab scenario: No risk tolerance = 15% Tolerate any risk = 3.3%</p> <p>Natalizumab scenario risk tolerance associated with: No disability = 1:100,000 versus wheelchair-bound = 1:1000 ($p < 0.0001$); Male = 1:2000 versus females = 1:10,000 ($p < 0.0001$); Patients caring for dependents = 1:50,000 versus not caring for dependents = 1: 10,000 ($p = 0.004$); Patients taking Natalizumab = 1:750 versus not taking Natalizumab = 1:10,000 ($p < 0.0001$); Patients who routinely use seatbelt = 1:10,000 versus those who do not routinely use seatbelt = 1:1000 ($p < 0.0001$)</p> <p>Common adverse effects (significance to reference): Increased risk of infection = reference Injection-site reactions = -0.16 Headaches, aches, flu = 0.02 Changes in mood = -0.82 ($p < 0.001$)</p> <p>Severe adverse effects: 0% = reference 1% = -1.15 ($p < 0.001$) 10% = 3.06 ($p < 0.001$) 30% = -3.82 ($p < 0.001$) Clinical outcomes – β coefficient values compared with baseline treatment profile: Prevents symptom progression for 1 year = 0.12 ($p < 0.001$); Prevents one relapse per year = 0.05; Prevents MRI progression for 1 year = 0.17 ($p = 0.002$)</p>
									Objective	Preference for treatment benefit: conjoint analysis	

(continued on next page)

Table 7 (continued)

First author (year)	Quality rating	Study design and methodology	Recruitment location	Sample size	Age (mean)	Type of MS (n)	DMD	Real/faux information	Self-report or objective measure	Outcome measure(s)	Results
											<p>Patient symptoms - β coefficient values compared with baseline treatment profile:</p> <p>Improved mildly = 0.81 ($p < 0.001$)</p> <p>Improved moderately = 0.83 ($p < 0.001$)</p> <p>Improved rarely but substantially = 1.03 ($p < 0.001$)</p> <p>Patients willing to accept 30% adverse risk for 32 years prevention of disease progression</p> <p>Preference for treatment risk-benefit profiles: conjoint analysis</p> <p>Objective</p> <p>Patients willing to accept 10% adverse risk for 25 years prevention of disease progression</p>

Absolute numbers reported, unless specified. Abbreviations: CIS, clinically isolated syndrome; DMD, disease-modifying drug; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; VAS, visual analogue scale. 1 = median, 2 = range.

their current medication could delay the progression of disease and just over 70% of MS patients were generally optimistic about their condition as a result of taking their current medication [41]. In two qualitative studies, MS patients taking first-line treatments described their medication as a “saviour” [34] and believed that taking the DMD felt as if they were “doing something progressive” towards their condition [35].

Only one early study employed an objective methodology to measure understanding of DMD benefits. Mohr and colleagues [36] administered a 12-item questionnaire prior to providing an intervention. Only 39% of MS patients accurately reported the benefits of taking their first-line DMD, and 57% of MS patients were found to optimistically and incorrectly state that MS relapses could be reduced by a half following uptake of their current DMD [36].

Acknowledging the difficulty in comparing studies with self-report and objective measures, and those encompassing MS patients taking a range of DMDs, the limited data in the current review indicates a general trend towards underestimation of treatment risks and overestimation of treatment benefits by MS patients during the routine healthcare system.

3.2. Results: secondary aim

3.2.1. Patient and study characteristics

The studies in this part of the review consisted mostly of surveys and questionnaires (see Table 7). One study that has previously been reviewed in the primary aim also included findings relevant to the secondary aim [43]. Only one study in this section of the review was found to have the strongest quality rating [46].

From the final 9 studies included into the secondary aim, a total of 7427 patients were included with a range of MS disease subtypes, comprising of: 45 (0.6%) CIS patients, 652 (8.4%) RRMS patients, 31 (0.4%) PPMS patients and 59 (0.8%) SPMS patients. Majority of the studies did not clearly report or specify the MS disease subtype (89.8%). The mean age of MS patients was 42 (range: 34–52).

Of the studies which reported the current DMDs of MS patients, majority reported patients taking first-line treatments, which includes interferons in five studies [43,47–50] and glatiramer acetate in four studies [47–50]. Patients taking more aggressive DMDs also formed a part of this review, specifically patients taking Natalizumab [48–51], Fingolimod [49,50] and Rituximab [49]. Two studies focused primarily on a single DMD [43,51].

3.2.2. Study outcomes

3.2.2.1. Preferences for treatment risks. Four studies, each employing objective methodologies, looked at MS patients' preferences for the risks of taking a treatment.

Tur and colleagues [48] assessed the level of risks that MS patients were willing to accept for hypothetical therapeutic scenarios. The authors also assessed the relationship between accepted levels of hypothetical treatment risks and current DMDs taken by MS patients. A visual analogue scale showed that MS patients on the aggressive treatment Natalizumab were willing to accept higher levels of hypothetical treatment risks in comparison to MS patients on any other DMD [48].

Hypothetical treatment scenarios were employed by two further studies using objective methodologies, which compared MS patients' preferences for different levels of treatment risks [49,50]. Both studies confirmed that DMDs with significant adverse side-effects were less preferred than DMDs with minor side-effects. In fact, both studies revealed that medications with no possibility of death or disability were significantly favoured to a medication with even a very low possibility (0.05% to 1%) of death or disability [49,50]. Mood changes were the only specific side-effect that would decrease the probability of taking a DMD by MS patients [49,50].

Using a standard gamble question task, another study employed a hypothetical treatment scenario which presented information about a

treatment that could cure MS, and a real treatment scenario which presented the risk profile of the aggressive DMD Natalizumab [52]. MS patients showed similar preferences for risks in both the hypothetical and real treatment risk scenarios, as adverse risks were accepted when in the range of 1 in 10,000 [52]. For the hypothetical treatment scenario, MS patients that were significantly likely to prefer higher levels of adverse risks were those presenting with the following characteristics: wheelchair bound, male, not responsible for dependents, not currently taking a DMD, taking Natalizumab and not routinely wearing a seatbelt for car travel [52]. With the exception of MS patients who were not taking a DMD, the same characteristics of MS patients preferred higher levels of treatment risks in the real DMD scenario [52].

Despite the comparison of hypothetical and real treatment risk profiles in this section of the review, MS patients showed similar low preferences for treatment risks.

3.2.2.2. Preferences for treatment benefits. MS patients' preferences for treatment benefits were assessed by five studies in the present review.

Two studies used subjective measures to assess the preferences of MS patients towards treatment benefits [43,46]. MS patients with a positive outlook towards their current DMD ranged from 20% to 90% within one study [43] and was approximately averaged at 60% in another [46]. Patient factors significantly associated with a positive attitude were patients with: lack of functional problem, no MS family history and knowledge of their current DMDs [43].

Turning to objective measures, Prosser and colleagues [47] utilised a gamble health outcomes task using hypothetical treatment scenarios to assess preferences of MS patients for treatment benefits. During this task, patients were required to choose either a drug offering a particular number of relapse-free days, or a drug offering a 50% chance of ending the MS relapse immediately but with 50% chance of the drug not working at all. On average, patients chose drugs likely to lead to 14.6 MS relapse-free days from the possible 29, implying a preference towards treatments offering moderate but guaranteed benefits. However, the authors did note that approximately 30% of MS patients chose an extreme number of relapse-free days, i.e. either 1 or 29 [47].

The frequency of MS relapses was also used as an outcome measure to assess MS patients' preferences for treatment benefits in the remaining two studies and was compared alongside other benefits that DMDs typically offer [49,50]. The highest preference for MS patients in one study was for substantial symptom improvement in MS, followed by prevention of disease progression over 10 years, mild symptom improvement and a five-year delay in MS relapses [50]. Administration in the form of an IV infusion or oral pill was also significantly preferred by MS patients. In fact, the ability to administer the drug orally was preferred even over a five-year delay in relapse [50]. Likewise, any form of improvement in symptoms and the ability to take the drug orally were also strongly preferred by MS patients in the latter study [49]. However, unlike the previous findings, MS patients in this study showed no significant preference for delay in MS relapses or administration of drugs via IV infusion [49]. Additionally, the ability to prevent MRI progression over the years was used as an indicator only in this study and was significantly preferred by MS patients [49].

Although all studies in this review assess MS patients' preferences for treatment benefits, chiefly for hypothetical treatment scenarios, the results are not directly equivalent as the range and actual treatment benefits offered to patients differed greatly between studies. In general, treatments offering high symptom improvement, a delay in disease progression, reduction in relapses and particular administration methods were preferred.

3.2.2.3. Preferences for treatment risk-benefit profiles. Three studies objectively measured the risk-benefit trade-off by offering MS patients the choice of benefits and risks for hypothetical treatments, using the conjoint analysis method [49–51]. Whilst all three studies used a similar objective methodology, the studies employed different treatment risk and

benefit scenarios. Johnson and colleagues [51] demonstrated that for a five-year delay of disease progression, a 0.48% risk of death by leukaemia was acceptable for MS patients; which increased to 1.08% for an eight-year delay of disease progression. For a similar delay of disease progression, the acceptable risk of death by liver failure increased by 0.53%, and acceptable risk of severe disability or death from PML increased by 0.36% [51]. Wilson and colleagues [50] found that patients were willing to accept 0.7% risk of developing PML given a delay in the progression of disease [50]. Up to 1% adverse risks were accepted by MS patients if substantial improvements in symptoms could be demonstrated by the treatment [50]. Patients were willing to accept up to 0.59% of severe adverse effects if drugs could be administered orally [50]. In fact, this level of risk acceptance was higher than for drugs which could delay the progression of MS by four years [50] or could reduce the frequency of MS relapses from four yearly to no relapses within the next five years [51]. Further, a risk of up to 30% of severe adverse effects was acceptable for MS patients given 32 years of delay in progression of MS [49].

The study by Bruce and colleagues also assessed risk and benefit trade-offs of hypothetical treatment scenarios, by using a Medical Decision Making Questionnaire (MDMQ) [53]. Similar to previous studies, the choice of whether to uptake a treatment for all patients differed significantly according to the combination of treatment risks and benefits [53]. Additionally, patients who were adherent to their current unspecified treatment were willing to take medications with significantly higher combinations of risks and benefits than patients who were assessed as non-adherent [53].

In summary, despite using similar measures to objectively assess trade-offs of treatment risks and benefits, the three studies employed very different combinations of risks and benefits, limiting any generalised conclusions that may be based on these findings. However, it was clear from these studies that preferred combinations of treatment risks and benefits play a key role in the choice of treatment.

4. Discussion and conclusion

4.1. Discussion

This systematic review was carried out to explore MS patient's understanding of DMD risks and benefits acquired through their standard healthcare systems, and MS patients' preferences for these risks and benefits; factors likely to impact shared decision-making. MS patients with different disease subtypes and those taking a range of DMDs were assessed by 22 studies in the present review. Understanding of DMD risks and benefits were mostly addressed as part of a larger project. MS patients' preferences for risks and benefits were generally assessed using treatments offering hypothetical risks and benefits. Studies employed both subjective and objective measures. The majority of studies had methodologies that precluded firm conclusions.

DMDs in MS have complex risk-benefit profiles. All DMDs offer benefits of varying levels, such as reduction in the frequency of MS relapses and delay in progression of the disease. Side-effects of treatments can range from mild symptoms to adverse effects that may lead to severe disability or death [3]. When making decisions about DMDs based on these complex risk-benefits, a shared decision-making approach is ideal.

For effective shared decision-making, clear and accurate DMD information should be provided to MS patients in order to facilitate understanding of treatment risks and benefits. Yet, it appears from the present review that MS patients do not sufficiently understand information about DMDs following routine consultations in their standard healthcare system. Despite evaluating their risk knowledge as high [18], MS patients in this review showed poor objective risk understanding [18,38]. There was a trend towards underestimation of treatment risks [40,44]. This is problematic for long-term treatment adherence, as some patients are more likely to initiate a treatment that they

perceive has lower risks but then discontinue treatment when the risks are higher than initially expected [19,22]. MS patients in this review were generally optimistic about the benefits of their current DMD [33, 34,40,46]. However, many patients overestimated the benefits of their DMD in reducing the frequency of relapses and delaying progression of disease [36,41]. This could mean that patients' optimism towards DMDs may not often accurately reflect the actual benefits of the drugs. This can further impact treatment adherence, since patients who do not accurately understand the benefits of DMDs are more likely to discontinue treatments overtime [22], perhaps as optimism for medications is replaced with the realisation that the medication does not offer expected levels of benefits. In fact, a significant relationship between patients who understand information about their treatments and their adherence to treatments is evident in several studies, including those in the present review [21,22,38,41]. Providing accurate and easily understandable risk and benefit information to MS patients should therefore improve treatment adherence towards their chosen treatment.

The ability to understand overall information about DMDs provided during the standard healthcare system was found to be associated with certain patient factors, for example: age, education and functional status [37,43]. It is also possible that symptoms of MS itself, for example depression [54], anxiety [55], fatigue [56] and cognitive impairments [57, 58], may further confound understanding of information about DMDs. However, these symptoms were not explored within the studies in this review. Regardless, it is apparent that some MS patients require further support to comprehend treatment information to a good standard. This may explain what prompts many patients to independently seek treatment data through sources beyond standard healthcare [19,41, 42]. This external treatment information may not necessarily be accurate or up-to-date and could lead to further misunderstanding. Thus future studies need to primarily focus on improving the existing methods of providing DMD information for all MS patients, in order to improve shared decision-making.

Effective shared decision-making also requires patients to communicate their preference for a particular treatment. Preferences specifically for risks and benefits of DMDs are likely to influence MS patients' treatment choice [24–26]. The secondary aim of the present review assessed the extent to which preferences towards risks and benefits that DMDs typically offer can impact MS patients' treatment decisions. As anticipated, even very low levels of adverse risks reduced patients' preference to take the treatment, and extremely small variations in risk had a significant impact on hypothetical treatment decisions [49,50,52]. Preference for medications with adverse risks rarely exceeded 1%. Preferences for risks also varied with certain patient factors, as higher risks were generally accepted by males, functionally impaired individuals, or people already taking aggressive treatments such as Natalizumab [48,52]. Similarly, certain benefits that DMDs typically offer were significantly preferred over others and had an impact on the choice of treatment. Remarkably, patients strongly favoured medications that could provide symptom improvement [49,50], which implies limited understanding for MS treatments since DMDs are not able to relieve symptoms of MS. To note, medications presented in both studies [49,50] employed hypothetical treatment scenarios and therefore it is plausible that patients perceived symptom improvement as hypothetical despite accurate understanding of DMD benefits [49,50]. It is nevertheless interesting that patients are likely to take higher risks if DMDs can seemingly aid symptoms of their condition. MS patients in this review also showed a greater preference for treatments offering large reductions in frequencies of relapses, longer delay in disease progression and drugs that could be administered orally, being prepared to accept a greater likelihood of risk in return [49–51,53]. Overall, MS patient preferences varied according to different combinations of particular risks and benefits, and had a significant impact on their choice of treatment. Thus, it is important to elicit patient preferences for particular risks and benefits of DMDs in order to improve shared decision-making in MS.

A limitation of the present systematic review is the difficulty in drawing robust conclusions or conducting a meta-analysis of the studies as a result of the variety of outcome measures employed. A narrative synthesis was considered to be the most appropriate format for reviewing the studies. However, it is important to acknowledge that such a qualitative review is subject to greater analysis bias than a quantitative systematic review. There were also differences in study design, methodology and patient characteristics between studies in the review, which limits conclusions from such findings. This reflects the lack of uniformity across studies that address MS patients' understanding of medications. The present review also does not constitute an exhaustive search of studies or research findings; for example, the primary authors of studies were not contacted to resolve or expand on study findings owing to time and resource constraints. However, it seems unlikely that supplementary results or additional outcome measures could produce less heterogeneous results.

4.2. Conclusion

The present review was the first to our knowledge to systematically gather evidence about patients' understanding of the risks and benefits of DMD during their standard healthcare system, and their preferences for these risks and benefits; factors which can likely impact shared decision-making. Despite the heterogeneous findings, it seems that current ways of providing DMD risk and benefit information are not generally uniform or effective. MS patients tend to underestimate treatment risks and overestimate treatment benefits, with some patients finding comprehension especially difficult. MS patients prefer treatments offering extremely low levels of adverse risks, but are willing to accept higher risks in exchange for substantial long-term improvements.

Practical implications of this review are providing extra support to ensure all patients are effectively informed about the complex risk-benefit profiles of MS DMDs, and ensuring patients' preferences for treatment risks and benefits are taken into account during the shared decision-making process.

Conflict of interest

GR has no disclosures.

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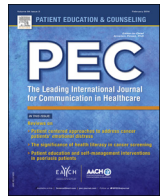
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Review article

Interventions to support risk and benefit understanding of disease-modifying drugs in Multiple Sclerosis patients: A systematic review

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ABSTRACT

Objective: The present review evaluates interventions that have been designed to improve understanding of the complex risk-benefit profiles of disease-modifying drugs (DMDs) in patients with Multiple Sclerosis (MS).

Methods: A systematic search conducted using PubMed, Embase, Google Scholar and PsycINFO identified 15 studies. Interventions which provided treatment information were present across a range of study designs. A narrative synthesis was conducted due to heterogeneity of research findings.

Results: Interventions providing treatment information ranged from comprehensive education programmes to booklets of a few pages. MS patients favoured the interventions they received. Understanding of overall treatment information and treatment risks specifically, generally improved following interventions. Yet overestimation of treatment benefits persisted. There was no conclusive effect on DMD decisions. No superior intervention was identified.

Conclusion: Interventions designed to improve understanding of DMD risk and benefit information are moderately successful.

Practice implications: Additional support provided to MS patients beyond routine healthcare can generally improve understanding of the complex risk-benefit profiles of DMDs. Future interventions need to ensure that patients with symptoms that may confound understanding can also benefit from this additional information.

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1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disorder of the central nervous system, which progresses at different rates between individuals [1]. MS patients experience a range of symptoms, including depression [2–4], anxiety [2,5], fatigue [3,6] and cognitive impairments [5,7,8], which likely confounds patients' general understanding and ability to recall important information. This could be problematic for MS patients when deciding a course of treatment.

The treatments currently available to MS patients are disease-modifying drugs (DMDs). Although DMDs do not target symptoms of MS, they can potentially reduce the number of relapses and delay progression of disease [9]. Yet the rate at which these benefits occur vary between DMDs and can even vary within individuals treated with the same medication. In general, MS patients are initially offered treatments with long-term safety profiles and limited adverse risks, but these are only moderately successful [10]. These treatments are also known as first-line DMDs. More aggressive treatments may be considered when initial therapies are not effective. DMDs at this stage offer higher benefits but potentially adverse effects, including leukaemia, cardiotoxicity, and progressive multifocal leukoencephalopathy (PML) [9–13]. MS patients are therefore faced with complex risk-benefit profiles of DMDs when deciding on the best course of treatment.

An understanding of the risks and benefits of treatments is one of the many components required for an effective shared treatment decision. Shared decision-making is a highly recommended concept in patient-centered healthcare and refers to the mutual exchange of information between patients and health professionals during decision-making, such as decisions made about the most suitable treatment course [14,15]. This approach is particularly suited to chronic conditions such as MS, where the risk-benefit profiles of treatments are complex and need to be effectively communicated in order to inform and engage patients

in treatment decisions [16,17]. Thus, it is reasonable to expect that improving MS patients' understanding of complex risk-benefit profiles of DMDs can have an impact on treatment decision-making.

To facilitate understanding, patients should ideally be presented with treatment options and treatment risk-benefit profiles in a clear and coherent manner [14,18]. Yet DMD information provided to MS patients during routine healthcare is not always clear or coherent [19–21]. This may explain why many MS patients actively seek DMD information elsewhere [22,23]. This external information may not be accurate or up-to-date, which could lead to further misunderstanding of treatment information. Interventions have been designed to provide information about the risks and benefits of DMDs that patients may seek beyond routine healthcare. Although such interventions aim to provide accurate information about DMD risks and benefits, it is also important to consider the way this information is presented. This is because understanding of treatment risks and benefits can be influenced by particular graphical [24–26] or numerical formats [27–29], the framing of information [30–32] and how comparisons of risks and benefits are communicated [33–35]. Thus, an ideal intervention will give patients unbiased and accurate treatment information using effective presentation methods in order to optimise the understanding of DMD risks and benefits, and consequently result in informed treatment decisions.

Köpke, Solari, Khan, Heesen and Giordano [36] recently reviewed 10 interventions designed to aid patient understanding of MS related information, which includes two interventions that specifically provided information about the risks and benefits of DMDs. Although all interventions reviewed were different in many respects, understanding of the disease generally improved post-intervention. Despite this improvement there was no conclusive effect on decision-making. This review, however, was limited to randomised controlled trials only, which does not allow for a comprehensive evaluation of all interventions that provide MS

Table 1
Search terms for systematic review.

Search terms
(Multiple AND Sclerosis)
AND
(patients OR people OR persons OR patient)
AND
(risk OR benefit OR side effect OR treatment OR medication OR therapy OR medicine OR medical OR therapies OR therapeutics OR pharmaceutical preparations)
AND
(format OR framing OR educating OR design OR informing OR health literacy OR strategy OR program OR intervention OR communicating OR information OR education OR learning)
AND
(perception OR understanding OR comprehension OR awareness OR knowledge OR decision-making)

information beyond routine healthcare, particularly information on the risks and benefits of DMDs [36].

To the best of our knowledge, the present systematic review is the first comprehensive evaluation of interventions primarily designed to improve understanding of risks and benefits of DMDs for MS patients. This review will also explore the effects of these interventions on patients' treatment decisions.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were used as guidelines for the presentation of this review [37]. A protocol for the present review was not previously published or registered.

2.1. Systematic literature search

The systematic literature search was conducted in November 2016 using PubMed, Embase, Google Scholar and PsycINFO. Uniform search terms were developed and used with all databases (see Table 1).

2.2. Eligibility criteria

The inclusion criteria for the studies in the present review were peer-reviewed studies in English, with human adults and with patients of any clinical subtype of MS. No date restriction was applied. Studies were not limited to any particular study design. No restrictions were placed on the type of control group. Studies were required to have interventions about either real DMD information or information about fictitious treatments which would eventually

support understanding of DMD information. Interventions were defined as any additional strategy or decision-aid which provided treatment information beyond that given during routine healthcare. Studies with some evaluation of these interventions were retained.

Studies were excluded if they evaluated educational interventions for complementary medicines or medications for the management of MS symptoms. Studies assessing patients' understanding for disease diagnosis or prognosis were not eligible for inclusion. Studies without any form of educational intervention, with interventions based on other aspects of MS such as cognition or self-management, interventions aimed primarily at health professionals, an intervention protocol for an upcoming study with no existing data, or interventions not exclusive to patients with MS, were also excluded from the review.

All titles and abstracts were screened. Studies that were considered relevant from additional reference checking were also included. At this stage, 96 studies were considered for eligibility and full texts were subsequently accessed (see Fig. 1).

2.3. Data extraction

Data extraction forms were created to extract relevant information from full texts, and assess their eligibility into the final review. Extraction was initially carried out by one reviewer (GR) and was verified by another (DL). Any discrepancies were resolved by discussion. Following data extraction, 81 studies were excluded from the final review in line with the exclusion criteria (see Fig. 1).

Baseline characteristics of participants were extracted from the 15 shortlisted studies, comprising (where reported) age, type of

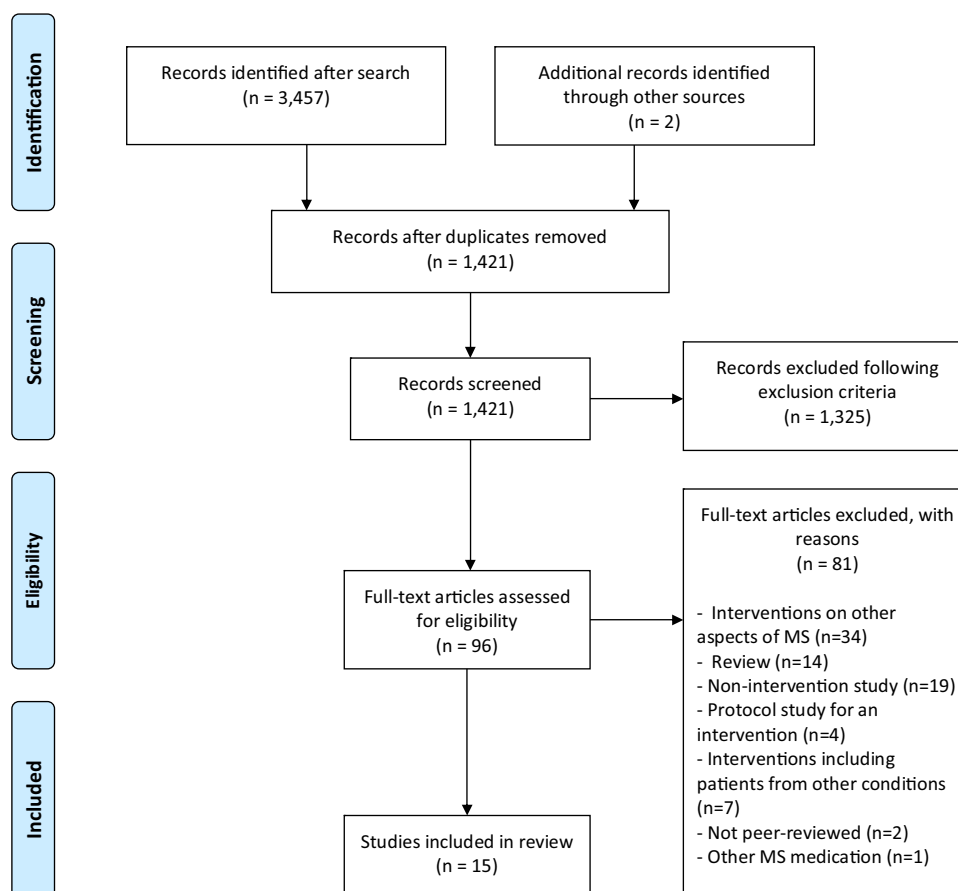


Fig. 1. PRISMA flow chart for selection process of studies in systematic review.

Table 2

Quality assessment of studies evaluating interventions to improve patient understanding of DMD information in MS.

Study (first author, year)	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropout	Overall quality rating
Mohr, 1996	Moderate	Moderate	–	Moderate	Strong	Strong	Strong
Kasper, 2006	Moderate	Moderate	Strong	Moderate	Strong	Weak	Moderate
Kasper, 2008	Strong	Strong	Strong	Strong	Moderate	Strong	Strong
Basso, 2010	Weak	Strong	Strong	Moderate	Strong	Moderate	Moderate
Heesen, 2010	Moderate	Moderate	Moderate	Weak	Moderate	–	Moderate
Kasper, 2011	Strong	Strong	Strong	Moderate	Moderate	Strong	Strong
Hofmann, 2012	Weak	Moderate	–	Moderate	Weak	Weak	Weak
Tur, 2012	Moderate	Weak	Strong	Moderate	Strong	Moderate	Moderate
Feicke, 2014	Moderate	Strong	Strong	Weak	Strong	Strong	Moderate
Köpke, 2014	Strong	Strong	Strong	Strong	Strong	Strong	Strong
Friedel, 2015	Moderate	Moderate	–	Moderate	Moderate	Weak	Moderate
Zimmer, 2015	Moderate	Moderate	–	Moderate	Moderate	Strong	Moderate
Colombo, 2016	Weak	Weak	–	Weak	Moderate	–	Weak
Kopke, 2016	Moderate	Strong	Strong	Moderate	Strong	Strong	Strong
Rahn, 2016	Weak	Strong	Strong	Moderate	Strong	Weak	Weak

Overall quality rating: Strong = no weak ratings; Moderate = one weak rating; Weak = two or more weak ratings.

MS, disease duration, time since diagnosis and current DMD. Study design and methodology was recorded. Information about the interventions was further extracted, including the content, length, presentation methods and any additional details of how the interventions were conducted.

The impact of the interventions on either understanding of treatment information overall or understanding of treatment risks and benefits specifically was also extracted in the present review and incorporates data from self-report and objective measures. Patient's feedback on the interventions was also retained. Relevant data for the present review was obtained from numerical information in texts, tables and graphs, and statistical analysis.

2.4. Quality assessment

Quality of publications was independently examined by two reviewers (GR and DL) using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies [38]. This particular tool was chosen because it can evaluate all types of quantitative studies in the health care setting [39], has high inter-rater reliability [39] and is often considered ideal for systematic reviews [40]. As per the tool, the final quality rating was derived from the rating of six measures: selection bias, study design, confounders, blinding, data collection methods, and withdrawals or drop-outs (see Table 2).

Quality was further assessed for educational interventions within the studies, based on their reporting of criteria for evidence-based patient information. Eight different criteria were chosen and adapted from Bunge and colleagues [18], depending on the extent of evidence and relevance to both simple and complex educational interventions (see Table 3).

3. Results

3.1. Study design and participant demographics

Fifteen studies were shortlisted in the review, and comprised interventions which were primarily designed to improve understanding of DMD risk and benefit information in MS patients. Four studies in this review evaluated interventions using a randomised controlled procedure [41–44]. A type of control group was present in seven studies [41,42,44–48] and baseline scores prior to the intervention were recorded by ten studies [42,43,47–53] (Table 4).

Five of the 15 studies were considered to be of a high quality [41–43,48,49], with three studies deemed weaker in quality [44,50,54] (see Table 2). Four of the 15 studies had interventions that fulfilled or reported at least 4 of the 8 criteria for evidence-based patient information. The most commonly reported criteria in

the interventions were the use of comprehension enhancing tools, involvement of patients in the development process and inclusion of numerical data (see Table 3).

A total of 2552 MS patients were included across 15 studies and had a range of MS disease subtypes, comprising: 79(3.1%) CIS patients, 1064 (41.7%) RRMS patients, 214 (8.4%) PPMS patients and 391 (15.3%) SPMS patients. The remaining MS patients had unclear or unreported MS disease subtype (31.5%). The mean age of patients was 43.1 years (range: 37–50). One study did not allow for calculation of mean age [49] and two studies only presented median or mode values for age [46,52]. Two studies also included 105 non-MS patients, with a mean age of 43.5 years [45,54].

Nine studies reported patients' disease duration from initial MS symptoms [42–44,46,47,50,53–55], with an average of 9.2 years. Five studies reported time since MS diagnosis [41,42,48,51,52], with an average of 5.8 years.

Only one included study reported patients' objective cognitive status [45]. Patients were assessed on the California Verbal Learning Test-II (CVLT-II), Wisconsin Card Sorting Test-64 (WCST) and the Digit Span subtest from Wechsler Adult Intelligence Scale. MS patients were considered to be cognitively impaired if they scored below the 5th percentile of at least one cognitive measure [45].

A total of 1384 (54.2%) MS patients had taken disease-modifying drugs during the course of their disease and 188 (7.4%) MS patients had not taken a DMD. The remaining studies did not specify DMD status (980 MS patients, (38.4%)). Of studies reporting MS patients' current DMD, 273 patients were on the first-line treatment interferon-beta [42,49,51], and the remaining patients were taking second-line treatments, with 53 patients on Mitoxantrone [50], 173 patients on Natalizumab [46,55] and 98 patients on Fingolimod [52]. In majority of these studies, DMD status was known by treating physicians or researchers involved with the study [46,47,49–52,55].

3.2. Intervention characteristics

3.2.1. Intervention type

The majority of interventions contained a booklet or leaflet for MS patients [41–44,46,48,50,51,53,55]. These leaflets ranged from providing comprehensive information (120 pages, [41,48]; 57 pages [42]) to short summaries [46,50,53]. The booklet length was unclear in four studies [41,44,51,55]. Four interventions which included booklets also contained an additional intervention component [41,42,48,51]. A short vignette of information was read aloud in one intervention but was not handed to patients in the form of a booklet or leaflet [45] (Table 5).

Table 3

Quality assessment of content and administration of evidence-based patient information: Criteria adapted from Bunge and colleagues (2010).

Study (first author, year)	Numerical data (e.g. frequencies)	Graphs (e.g. bar chart, pictograph)	Balanced framing	Pictures and drawings	Clear layout (e.g. size of font)	Plain language and readability	Comprehension enhancing tools (e.g. mind maps)	Development process (e.g. feedback from patients)
Mohr, 1996	X	–	–	–	–	–	–	–
Kasper, 2006	X	X	–	–	–	X	–	X
Kasper, 2008	X	X	X	–	X	X	–	X
Basso, 2010	–	–	–	–	–	X	X	–
Heesen, 2010	–	–	–	–	–	–	–	–
Kasper, 2011	–	X	–	X	–	–	–	–
Hofmann, 2012	X	–	–	–	X	–	–	–
Tur, 2012	–	–	–	–	–	–	–	X
Feicke, 2014	–	–	–	–	–	–	X	X
Köpke, 2014	–	–	–	–	–	–	X	X
Friedel, 2015	–	–	–	–	–	–	X	–
Zimmer, 2015	–	–	–	X	–	X	X	–
Colombo, 2016	X	X	–	–	X	X	X	X
Köpke, 2016	–	–	–	–	–	–	X	X
Rahn, 2016	X	–	–	X	–	–	X	X

X = criteria reported; – = criteria unreported or not present.

Multicomponent educational programmes were utilised as an intervention in five studies. Four of these programmes were conducted by health professionals [48,49,51,52] and one education programme was conducted by a non-medical person [42].

3.2.2. Intervention content

All, bar two interventions [49,53], provided some form of treatment risk information to patients with MS. Interventions also included information about: treatment benefits [36,41,43,45,47–49,53,54], alternative DMDs available to patients [42,45,47,48], efficacy studies for DMDs [42,48,52–54], DMD decision-making [41,42,48,54], administration of DMDs [51,52,54] and tailored information about DMDs for patients' disease subtype [41,55].

3.2.3. Intervention presentation methods

Many different methods to present information were employed in the interventions. Methods which provided numerical information was manipulated by some studies, for instance by presenting or giving explanations for absolute risk numbers [41,43,50,53], relative risk numbers [43] and confidence intervals [44]. Four studies used graphical formats in the form of either pictograms [41,43,53] or bar graphs to convey treatment information [54]. One study focused on whether the information was framed in a positive or negative manner [41].

Some interventions also provided treatment information using interactive methods, defined as involving patient in the intervention process, which includes: questions and answers [42,47,48,51], discussions in person [42,47,48,51], role-playing [48], recognition cues [45], information presented in short successions [45] and interactive exercises presented at the end of interventions [41,42,47,52]. Media and technology was used to present treatment information in two studies [36,48,49,54].

Together, these strategies were designed to optimise understanding of the risks and benefits of DMDs.

3.3. Intervention outcomes

3.3.1. Understanding of overall treatment information

Four studies looked at understanding of overall treatment information with no particular focus on the risks or benefits of treatments. All employed an objective comprehension questionnaire to assess understanding, but maximum scores ranged from 6 to 18 (Table 6).

Despite no significant difference in the understanding of treatment information between a non-clinical control group and MS patients without cognitive impairment, both groups were significantly better than cognitively impaired MS patients [45]. The control and MS cognitively unimpaired group showed greater understanding following information provided in short successions or when recognition cues were provided to aid recall of information, compared to when treatment information was provided in an uninterrupted block [45]. A similar trend was observed in the cognitively impaired MS group. However, this group also showed a significant improvement in understanding when recognition cues were given alongside treatment information provided in short successive steps, in comparison to information provided in successive steps alone [45]. In two other studies, a significant increase in understanding of overall treatment information was also evident following intervention when compared to both baseline understanding [52] and a control group receiving standard information [44]. However, there was no significant improvement on patients' understanding post-intervention when the control group received identical content as the intervention in a non-interactive form [47].

To note, studies differed in the content of the intervention, as only two of the four studies provided information about real DMDs [47,52]. Further, only some items in the questionnaires used to assess patients' understanding focused specifically on treatment-related information.

In summary, although there is a trend towards an improvement in understanding of overall treatment information following intervention, this cannot be established with studies employing different interventions and comparison groups.

3.3.2. Treatment risk understanding

The understanding of treatment risks in MS patients following intervention was assessed by five studies, using real DMD information in four studies [42,48,50,54] and a hypothetical treatment information in another [43].

Following a short leaflet about risks of taking Mitoxantrone, MS patients showed a significant increase in accurate risk understanding of Leukaemia, an adverse risk associated with the medication [50]. This risk was initially underestimated by 58% of MS patients [50]. Underestimation of risk persisted in 18% of MS patients following intervention. Improved risk understanding was not dependent on demographic factors, disease duration or the

Table 4

Study design and participant demographics.

Study (first author, year)	Quality ratings	Methodological design	Recruitment method	Sample size	Mean age in years	Type of MS (n)	Disease duration and time since diagnosis (years)	Current DMD status	Real/faux risk-benefit information
Mohr, 1996	Moderate	Pre-post intervention study	Outpatient clinics	99	–	Not specified	–	Interferon beta-1b	Real
Kasper, 2006		Pre-post intervention study	Outpatient clinics	169	44	RRMS (75); PPMS (75); Unclear (19)	Disease duration (7.7)	DMD (103); No DMD (66)	Real
Kasper, 2008	Strong	Double-blind RCT	Newspapers; web-sites; National self-help journal	297	43	CIS (45); RRMS (153); PPMS (31); SPMS (59); Unclear (9)	Time since diagnosis: IG (8.9) CG (8.3)	Not specified	Real
Basso, 2010	Moderate	Questionnaire	Newspapers; Newsletter of MS society; MS support groups	36	MS patients without cog impairments (48); MS patients with cog impairment (45); CG (38)	RRMS (14); Unclear (22);	–	Not specified	Real – Unrelated to DMD
Heesen, 2010	Moderate	Questionnaire	MS outpatient clinics	69	40 ^a	Not specified	Disease duration (11)	Natalizumab	Real
Kasper, 2011	Strong	RCT	MS outpatient clinic; Centre of Neurology; MS society	111	43	Not specified	Disease duration (7.5)	Not specified	Faux
Hofmann, 2012	Weak	Retrospective cohort study	Patients allocated Mitoxantrone in last 9 years (<i>database of hospitals and private clinics</i>)	575	50	RRMS (49); PPMS (76); SPMS (258); Other (4); Unclear (188)	Disease duration (28.9)	Mitoxantrone (53); Terminated Mitoxantrone (522)	Real
Tur, 2012	Moderate	Survey	MS clinics	104	JCV seropositive (38); JCV seronegative (37)	RRMS	Disease duration: JCV positive (13.72) JCV negative (11.73)	Natalizumab	Real
Feicke, 2014		Quasi-experimental study design	MS clinics; private practise	64	IG (42); CG (37)	RRMS (35); PPMS (2); SPMS (2); Unclear (25)	Disease duration: IG (0.97) CG (1.64)	DMD (45); No DMD (19)	Real
Kopke, 2014	Strong	Double-blind RCT	MS outpatient clinics	192	37	CIS (27); RRMS (133); Unclear (32)	Disease duration: IG (4.3) CG = 4.0 Time since diagnosis: IG (1.4) CG (1.2)	Not specified	Real
Freidal, 2015	Moderate	Prospective longitudinal study	MS clinics	174	40	RRMS (125); Unclear (49)	Time since diagnosis (4.84)	Interferon-beta 1b Previous DMD (82); No previous DMD (75)	Real
Zimmer, 2015	Moderate	Pre-post intervention study	MS Centre	98	41 ^b	Unclear	Time since diagnosis (4.6 ⁴)	Fingolimod Previous DMD (67); No previous DMD (31)	Real
Colombo, 2016		Survey	Press release; Website adverts; Newsletters; E-mail invitations; Meeting presentations	344 MS patients (276) Family reporting about MS patients (68)	MS patients (43); Family reporting about MS patients (45)	MS patients: RRMS (203); PPMS (12); SPMS (32); Unclear (29) Family reporting about MS patients: RRMS (26); PPMS (3);	Disease duration: MS patients (9); Family reporting about MS patients (9)	DMD not specified	Real

Table 4 (Continued)

Study (first author, year)	Quality ratings	Methodological design	Recruitment method	Sample size	Mean age in years	Type of MS (n)	Disease duration and time since diagnosis (years)	Current DMD status	Real/faux risk-benefit information
Kopke, 2016		Prospective controlled trial	Rehabilitation centres	156	IG (42); CG (43)	SPMS (13); Unclear (26) CIS (5) RRMS (105); PPMS (13); SPMS (14); Unclear (19)	Time since diagnosis: IG (7) CG (9)	DMD (88); No DMD (68)	Real
Rahn, 2016		Pilot RCT	MS day hospital; MS self-help society; Other self-help initiatives	64	IG (47); CG (44)	CIS (2) RRMS (42); PPMS (2); SPMS (13); Unclear (5)	Disease duration: IG (9); CG (10)	DMD (29); No DMD (35)	Faux

Absolute numbers reported, unless specified. Abbreviations: CG, Control group; CIS, clinically isolated syndrome; Cog, Cognitive; DMD, Disease-modifying drug; IG, Intervention group; MS, Multiple Sclerosis; PPMS, primary progressive multiple sclerosis; RCT, Randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

^a Mode value.

^b Median value.

available scientific evidence at treatment initiation. However, patients with large errors on the Medical Data Interpretation Test (MDIT), which assessed the ability to handle probability data, showed an underestimation of Leukaemia risk after reading the leaflet [50]. Following an intervention with a 4-h education programme combined with a 57-page leaflet, understanding of the first-line DMD risks significantly improved for patients in the intervention group compared to MS patients in the control group [42]. The authors further combined the scores of risk understanding with patient's attitude towards their current DMD, which they termed as the score of being informed. According to this measure, patients in the intervention group were significantly better informed than the control group [42]. Similar results were seen with another multi-component intervention, consisting of a 2-h and 4-h education programme, in addition to a 120-page information brochure [48]. In comparison to the control group receiving standard information brochure and a rehabilitation programme, the intervention group showed a significant increase in DMD risk understanding at 2 weeks and 6 months post-intervention [48].

One study measured risk understanding using self-report questions after trialling a DMD informational website for interferons [54]. Over 80% of MS patients stated that they found the presented risk information really or extremely clear and easy to understand [54].

Using hypothetical treatment information, Kasper and colleagues [43] showed that the ability to recall treatment risks from pictograms to frequencies was generally low. However the authors noted that risks were recalled more accurately than benefits [43]. Mean errors in recalling risks from pictograms which displayed figures consecutively were significantly lower as opposed to pictographs with random arrangement of figures [43]. Patients that attributed high personal risk of becoming wheelchair dependent within two years showed a small correlation with overestimation of risk following intervention [43].

Overall, understanding of treatment risks showed an improvement of reasonable accuracy post-intervention despite the variety of interventions employed across the reviewed studies, and studies using a mixture of self-report and objective measures.

3.3.3. Treatment benefit understanding

Understanding of treatment benefits was assessed objectively by four studies post-intervention [43,46,49,53] and with self-report measures by one study [54].

Following a 3-page information booklet, MS patients showed significant improvements in understanding of interferon benefits post-intervention when compared to baseline [53]. The authors did note that around 99 of 169 patients were still not able to understand the information after intervention [53]. Following another educational intervention, there was a significant reduction in patients that were overly optimistic about the general benefits of their DMD, even though overestimation persisted in about 33% of individuals [49]. At baseline, approximately 34% of MS patients were unrealistically optimistic about the benefits of their medication on disease progression specifically. Yet post-intervention, the number of MS patients overestimating these specific benefits about their DMD increased to about 40% [49]. Likewise, in another study, MS patients believed that their medication will provide a greater reduction of risk for a maximum walking distance of 100m following the short leaflet-based intervention on Natalizumab, in comparison to physicians [46]. Even with hypothetical treatment information, MS patients overestimated the benefits of a fictitious treatment by more than 100% following intervention [43].

Using self-report measures, over 75% reported that the interferon benefits presented in a DMD informational website were really or extremely clear and that graphical presentations of treatment benefits were easy to understand [54].

In summary, initial overestimation of treatment benefits seemingly persists despite interventions that provide treatment benefit information beyond routine healthcare, although many patients report their own understanding of treatment benefits following intervention as high.

3.3.4. Personal risk perception

Beyond understanding of treatment risk, two studies also assessed personal perception for treatment risks following interventions that provided information about real DMDs [46,50].

Following a short leaflet about Natalizumab, 84% of MS patients were willing to accept a 1 in 100 or higher risk of PML, an adverse side-effect of the medication, compared to only 51% of physicians; showing a significant difference [46]. The authors noted that PML risk acceptance was not correlated with understanding of DMD information [46]. Patient's personal risk attribution of PML as an adverse risk of Natalizumab was deemed significantly lower than the PML risk they attributed to Natalizumab generally post-intervention [46]. However, since baseline measures were not recorded in the study, it is difficult to determine whether personal

Table 5

Outcomes of DMD informational interventions.

Study (first author, year)	Intervention type	Control group	Intervention content	Intervention presentation format	Baseline recorded	Self-report or objective measure	Outcome measure	Results
Mohr, 1996	Education session (conducted by a MS Nurse)	None	Information about treatment benefits	Videotape	Yes	Objective	DMD benefit understanding: Survey items from BSQ (follow up: immediate)	Relapse rate: Expected < 10% reduction ('overly pessimistic group'); Baseline = 4% patients; Post-intervention = 1% patients Expected 10–30% reduction ('accurate group'); Baseline = 39% patients; Post-intervention = 66% patients Expected >50% reduction ('overly optimistic group'); Baseline = 57% patients; Post-intervention = 33% patients Disease progression: Expected no change: Baseline = 40% patients; post-intervention = 20% Expected slower progression: Baseline = 26% patients; post-intervention = 41% Expected some restoration of function: Baseline = 29% patients; post-intervention = 37% Expected return to normal function: Baseline = 4% patients; post-intervention = 2%
Kasper, 2006	3-page information booklet	None	Interferon DMD benefits; Clinical trial information about interferons	Control event rate; Experimental event rate; Absolute risk reduction; Pictograms	Yes	Objective	DMD benefit understanding: Three items (follow up: immediate)	Control event rate: Pre-intervention = 10% Post-intervention = 43% Significant difference ($p < 0.001$) Experimental event rate: Pre-intervention = 33% Post-intervention = 43% Significant difference ($p = 0.043$) Absolute risk reduction: Pre-intervention = 21% Post-intervention = 41% Significant

Table 5 (Continued)

Study (first author, year)	Intervention type	Control group	Intervention content	Intervention presentation format	Baseline recorded	Self-report or objective measure	Outcome measure	Results
Kasper, 2008	120-page new Information booklet; Worksheet	80-page booklet of routinely available information	Basics of how risks are presented; Tailored approach to disease subtype; Risk-benefits of DMD; Decision-making	Probabilities; Absolute numbers; Pictograms of risks and benefits; Positive and negative framing; Interactive exercise	Yes	Self-report	Evaluation of intervention: VAS (<i>follow up: >6 months</i>) DMD decisions: VAS (<i>follow up: baseline, >4 week, >6 month</i>)	difference ($p < 0.001$) IG = rated value of information higher than CG ($p < .001$) IG = better informed than CG ($p < .001$) IG = felt more important questions were answered adequately than CG ($p < .001$) Positive attitude of current DMD: Baseline: CG = 62%; IG = 65% Post-intervention: IG more critical towards DMD than CG (> 4 week; $p < 0.008$) Progress in decision: No sig difference between IG and CG Uninterrupted (mean score): CG ($n = 12$): 8.63 MS-unimpaired ($n = 24$): 7.79 MS-cog impaired ($n = 12$): 5.58 Information read aloud in 'chunks' (mean score): CG: 9.94 MS-unimpaired: 8.96 MS-cog impaired: 8.25 Information read aloud in 'chunks' with recognition cues (mean score): CG: 9.88 MS-unimpaired: 9.38 MS-cog impaired: 9.33 CG: Chunking and recognition cueing better than uninterrupted ($p < 0.001$) MS-unimpaired: Chunking and recognition cueing better than uninterrupted ($p < 0.001$) MS-cog-impaired: Recognition cueing better than chunking and uninterrupted; chunking better than uninterrupted ($p < 0.001$)
Basso, 2010	Treatment disclosure vignette (5 paragraphs of 2–5 sentences each)—read aloud to people with MS	Treatment –disclosure vignette (5 paragraphs of 2–5 sentences each)—read aloud to healthy people	Information about treatment; Treatment benefits and its likelihood; Treatment risks and likelihood; Alternative treatments and their risks-benefits	1. Information read aloud uninterrupted; 2. Information read aloud in 'chunks' without recognition cues 3. Information read aloud in 'chunks' with recognition cues	No	Objective	General understanding of information: comprehension questions (max. 10 points) (<i>follow up: immediate</i>)	Uninterrupted (mean score): CG ($n = 12$): 8.63 MS-unimpaired ($n = 24$): 7.79 MS-cog impaired ($n = 12$): 5.58 Information read aloud in 'chunks' (mean score): CG: 9.94 MS-unimpaired: 8.96 MS-cog impaired: 8.25 Information read aloud in 'chunks' with recognition cues (mean score): CG: 9.88 MS-unimpaired: 9.38 MS-cog impaired: 9.33 CG: Chunking and recognition cueing better than uninterrupted ($p < 0.001$) MS-unimpaired: Chunking and recognition cueing better than uninterrupted ($p < 0.001$) MS-cog-impaired: Recognition cueing better than chunking and uninterrupted; chunking better than uninterrupted ($p < 0.001$)
Heesen, 2010	3-page leaflet	3-page leaflet given to physician's	Information about natalizumab-associated PML	Unclear	No	Self-report	DMD benefit understanding: average (<i>follow-up: immediate</i>)	Risk of maximum walking distance of 100 m after Natalizumab: Patients = 40% to 10%

Table 5 (Continued)

Study (first author, year)	Intervention type	Control group	Intervention content	Intervention presentation format	Baseline recorded	Self-report or objective measure	Outcome measure	Results
Kasper, 2011	Booklet	None	Risk-benefit profiles of a faux DMD: 'Relevant scenario' (<i>related to medication</i>) Risk-benefit of non-medical problem: 'Neutral scenario' (<i>not related to medication</i>)	Pictograms showing risks-benefits without numerical or verbal explanation; Graphical explanation of absolute and relative risk reduction; Graphical explanation of benefit vs. no-benefit of DMD	No	Self-report	DMD risk understanding: VAS (<i>follow-up: immediate</i>)	Physicians = 10% to <10% 10-year risk of being wheelchair-bound after Natalizumab: Patients = 40% to 10% Physicians = 30% to 10% Progression free after 2 years of Natalizumab: Patients = 50% Physicians = 50% Patient's general PML risk attribution = 4.5 No significant difference with physician
						Self-report	DMD risk perception: 4 risk options and VAS (<i>follow-up: immediate</i>)	Stop Natalizumab at following risk levels of PML: 2:10,000: Patients = 17%; Physicians = 49% 1:100: Patients = 29%; Physicians = 48% >1:100: Patients = 29%; Physicians = 3% Patient's personal PML risk attribution = 2.7
						Self-report	DMD decisions: VAS (0–10) (<i>follow-up: immediate</i>)	Willingness to continue treatment (mean VAS score): Patients = 9.0 Physicians = 6.1
						Objective	DMD risk understanding of 'relevant scenario' (<i>related to medication</i>) (<i>follow-up: immediate</i>)	Mean errors of frequencies of side-effects: 'Unsorted pictogram' group = 15.7% (s.d. 12.4) 'Sorted pictogram' group = 10.8% (s.d. 9.6) Total = 11.4%; Mean error = +15.0
							DMD benefit understanding of 'relevant scenario' (<i>related to medication</i>) (<i>follow-up: immediate</i>)	Mean errors of frequencies of benefits: 'Unsorted pictogram' group = 20.2% (s.d. 20.4) 'Sorted pictogram' group = 16.8% (s.d. 16.1) Total = 16.5%; Mean error = +17.7
							DMD decisions: (<i>follow up: immediate</i>)	No correlation between DMD choice and understanding of treatment information
						Self-report	Evaluation of intervention: Preference for pictograms	Preference for 'unsorted pictograms' = 2%

Table 5 (Continued)

Study (first author, year)	Intervention type	Control group	Intervention content	Intervention presentation format	Baseline recorded	Self-report or objective measure	Outcome measure	Results
Tur, 2012	Booklet	None	Risk factors of PML; Risk of discontinuing Natalizumab; Tailored to individual PML risk	Unclear	No	Self-report	(<i>follow up: immediate</i>) DMD decisions: discontinuation of Natalizumab treatment (<i>follow up: immediate</i>)	Patients with highest PML risk = 60% discontinued treatment Patients with second-highest PML risk = 24% discontinued treatment Patients JCV seronegative = 0% discontinued treatment Patients JCV seropositive for less than 2 years = 0% discontinued treatment
Hofmann, 2012	5-min leaflet	None	Summary of LK and CT risks; General risk knowledge of Mitox	Absolute risk numbers; Probability data	Yes	Objective	DMS risk understanding: Risk choice from 4 options (<i>follow-up: immediate</i>)	Risk of Leukemia: Baseline estimation of risk: Accurate risk at 8:1000 = 40% Underestimation of risk at 8:10,000 = 58% Overestimation of risk = 1% Post-intervention estimate of risk: Accurate risk at 8:1000 = 79% Underestimation of risk at 8:10,000 = 18% Overestimation of risk = 4% Post-intervention: Significant increase of risk perception for Leukemia and cardiotoxicity ($p < .05$)
						Self-report	DMD risk perception: General risk perception and individual risk perception using VAS (<i>follow-up: immediate</i>)	Baseline and post-intervention: General risk perception higher than individual risk perception ($p < .001$). Intervention considered important by most patients = 1.1 median VAS rating Intervention did not increase worries = 4.7 median VAS rating Recommend intervention to others = 85% Mean score at baseline: CG = 10.70 IG = 10.77 No significant difference
Feicke, 2014	420 min training program (<i>conducted by trained neurologist, psychologists or MS Nurse</i>)	Brochure with same content as training	Seven modules including: Risks and benefits of DMDs; DMD options; General info about DMDs	Discussions; Mind maps; rating scales; interactive exercises; Q&A	Yes	Objective	General understanding of information: 14 comprehension questions (<i>follow up: baseline,</i>	

Table 5 (Continued)

Study (first author, year)	Intervention type	Control group	Intervention content	Intervention presentation format	Baseline recorded	Self-report or objective measure	Outcome measure	Results
							immediate, > 6 month)	Mean score post-intervention (immediate): CG = 11.61 IG = 12.52 No significant difference Mean score post-intervention (> 6 months): CG = 11.88 IG = 11.77 No significant difference Mean risk knowledge at baseline; IG = 10.6 CG = 9.4 Mean risk knowledge (> 2weeks): IG = 12.3 CG = 10.2 Significant difference (p < .001) IG more critical of DMDs than CG; IG felt less social pressure towards DMD uptake DMD status (> 6 months) IG (n = 41): Newly initiated DMD = 16 Discontinued = 5 CG (n = 51) Newly initiated DMD = 18 Discontinued = 12
Kopke 2014	57-page new educational booklet; 4-h education programme (conducted by a non-medical person)	5 page information leaflet; 4-h education programme for stress management in MS	Recent evidence of early MS DMD; DMD efficacy studies; DMD options in early MS; Risks-benefits of DMDs in early MS; Decision-making exercise and discussion	PowerPoint presentation; Q&A; Group discussion; Guided discussion; Interactive exercises	Yes	Objective	DMD risk understanding: 19-item questionnaire (follow-up: baseline; >2 weeks)	Mean patient ranking: Satisfaction with medication application (n = 114) = 1.11 Satisfaction with injection training (n = 111) = 1.23 Satisfaction with telephonic care (n = 58) = 1.43 Intervention useful? Yes = 64 Little = 16 No = 3 Median score (maximum 18): Pre-test = 6 Post-test = 14
						Self-report	DMD decision-making: PBMS (follow-up: 2 weeks, 6 and 12 months)	Perception of being informed: Pre-intervention: Score < 7 = 78; Score > 7 = 19 Post-intervention: Score < 7 = 0; Score > 7 = 97 Certainty of being able to handle all treatment:
Freidal, 2015	Practical education; telephone consultations; home visits; (conducted by MS Nurses); written guide; DVD	None	Injection techniques; management of side-effects; storage and transportation; possible side-effects; importance of adherence	Q&A; private telephone and home consultations	Yes	Self-report	Evaluation of intervention: 6-point likert scale (1 = very good to 6 = insufficient) (follow-up: >3 months)	
Zimmer, 2015	60-minute talk for treatment-experienced patients; 90-minute talk for newly diagnosed patients; text and picture cards; take-home manufacturers leaflet (conducted by MS Nurse)	None	Efficacy and mode of action; administration, pauses and non-adherence; storage; pharmacy, costs and insurance; side-effects and how to understand information leaflet; risks and prevention; monitoring over time	Interactive talk; text cards with pictures to accompany talk; 'memory cards' at end with key points	Yes	Objective	General understanding of information: questionnaire (follow-up: immediate)	
						Self-report	Evaluation of intervention: VAS (0 = not at all informed, to 10 = totally informed) (follow-up: immediate)	

Table 5 (Continued)

Study (first author, year)	Intervention type	Control group	Intervention content	Intervention presentation format	Baseline recorded	Self-report or objective measure	Outcome measure	Results
Colombo, 2016	Website	None	Interferon DMD benefits; Interferon DMD risks; Strength of evidence; Areas of uncertainty; Long-term adverse effects; Glossary; Patient stories; Description of participant characteristics from clinical trials; Questions to ask neurologists; Practical information about interferons	Short and detailed info; Bar graphs; frequencies; verbal info in tables	No	Self-report	DMD benefit understanding (follow-up: immediate)	Pre-intervention: Score < 7 = 64; Score > 7 = 33 Post-intervention: Score < 7 = 1; Score > 7 = 96 Confidence in being able to handle all treatment aspects: Pre-intervention: Score < 7 = 19; Score > 7 = 78 Post-intervention: Score < 7 = 1; Score > 7 = 96 Interferon benefits clear? (n = 304) No = 6% Somewhat = 19% Really/extremely = 75% Graphic presentation of interferon benefits easy to understand? (n = 304) No = 3% Somewhat = 18% Really/extremely = 79% Interferon risks clear? (n = 304) No = 4% Somewhat = 12% Really/extremely = 84% Tables of interferon risks easy to understand? (n = 304) No = 3% Somewhat = 12% Really/extremely = 85% Confident about interferon decision? (n = 286) No = 9% Somewhat = 29% Really/extremely = 62% Website easy to navigate? (n = 418) No = 2% Somewhat = 5% Really/extremely = 93% Information easy to understand? (n = 433) No = 1% Somewhat = 12% Really/extremely = 87% Information useful? (n = 433) No = 2% Somewhat = 14% Really/extremely = 84% Adequate risk knowledge: (> 8 correct answers): Baseline:
Kopke, 2016	120-page information brochure; 2-h education programme; 4-h education programme	Printed information material; standard	Information about evidence of DMDs; Decision-making with consultants;	Powerpoint presentations; Discussions; Q&A; role-play	Yes	Objective	DMD risk understanding (follow up:	

Table 5 (Continued)

Study (first author, year)	Intervention type	Control group	Intervention content	Intervention presentation format	Baseline recorded	Self-report or objective measure	Outcome measure	Results
	(programme conducted by 2 trained MS nurses or psychologists)	rehabilitation programme	Risks and benefits of new oral therapies				baseline, >2 weeks, >6 months)	CG = 22.5% IG = 20.6% 2-weeks post intervention: CG = 31% IG = 54.1% Significant difference from baseline ($p < .007$) 6-months post intervention: CG = 31.2% IG = 48.2% Significant difference from 2 weeks ($p = 0.058$) Mean risk knowledge (0–19): Baseline: CG = 6.51 IG = 6.06 Non-significant difference ($p > .05$) 2-weeks post intervention: CG = 7.31 IG = 8.85 Significant difference ($p < .004$) 6-months post intervention: CG = 7.12 IG = 8.05 Non-significant difference ($p > 0.05$) Improvement in risk knowledge (> 2 weeks to >6 months): CG = 0.59 IG = 2.52 Significant difference ($p < 0.001$) Improvement in risk knowledge (baseline to >6 months): CG = 0.46 IG = 2.12 Significant difference ($p = 0.002$) Mean correct answers: CG = 3.8 IG = 4.8 Significant difference ($p = 0.002$) Understandable? CG = 4.5 IG = 6.5 Relevant? CG = 6.6 IG = 7.6 Improvement in subjective knowledge? CG = 4.8 IG = 6.6
Rahn, 2016	Patient information materials	Standard information	Explanation of confidence intervals, used to explain DMD risks and benefits	An example story to explain confidence intervals (unrelated to MS)	No	Objective	General understanding of information: 6 questions (follow up: immediate)	Significant difference ($p = 0.002$) Mean correct answers: CG = 3.8 IG = 4.8 Significant difference ($p = 0.002$) Understandable? CG = 4.5 IG = 6.5 Relevant? CG = 6.6 IG = 7.6 Improvement in subjective knowledge? CG = 4.8 IG = 6.6
						Self-report	Evaluation of intervention: Likert scale (1 = not at all, to 10 = very) (follow up: immediate)	Understandable? CG = 4.5 IG = 6.5 Relevant? CG = 6.6 IG = 7.6 Improvement in subjective knowledge? CG = 4.8 IG = 6.6

Table 5 (Continued)

Study (first author, year)	Intervention type	Control group	Intervention content	Intervention presentation format	Baseline recorded	Self-report or objective measure	Outcome measure	Results
								Beneficial intervention? CG = 6.0 IG = 7.8

Absolute numbers reported, unless specified. Abbreviations: CG, Control group; CIS, clinically isolated syndrome; Cog, Cognitive; CK, Cardiotoxicity; DMD, Disease-modifying drug; IG, Intervention group; LK, Leukemia; MDMIC, Multi-Dimensional Measure of Informed Choice; MS, Multiple Sclerosis; PBMS, Planned Behaviour in MS questionnaire; PML, progressive multifocal leukoencephalopathy; PPMS, primary progressive multiple sclerosis; Q&A, Questions and answers; RCT, Randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; VAS, visual analogue scale; UTD, Understanding Treatment Disclosure Scale.

risk attribution changed as a result of the intervention or was previously low at baseline. In another study which did record baseline measures, MS patients showed a significant increase from baseline for both general and personal risk attribution of the adverse risks associated with Mitoxantrone after reading the informational booklet [50]. Yet similar to the previous study, personal risk attribution of the adverse risks of the DMD was significantly lower than general attributed risk of adverse risks by the MS patients [50].

In summary, two studies show that patients attribute lower personal risks of taking their current DMD than general risks they attribute to the DMD, despite improved understanding of their DMD risks post-intervention.

3.3.5. Treatment decisions

Five studies recorded MS patients' decision or their attitude for decisions for their current DMD following intervention [41,42,46,54,55].

Using self-report likert-scales, MS patients in the intervention group were found to be significantly more critical about their current DMD compared to baseline and control group, even after four weeks following intervention [41]. Likewise, patients were critical towards current DMD after intervention in another study although this attitude did not persist beyond two weeks [42]. In another study, patients reported feeling confident in their decision to choose interferons after receiving information about interferons beyond routine healthcare [54].

MS patients in the intervention group did not show significant differences to the control group in progress of DMD decisions during follow-up in two studies [41,42]. When compared with physicians' decisions however, a considerably higher number of patients opted to continue the Natalizumab DMD post-intervention [46]. Although for the same medication following another intervention, 60% of MS patients discontinued treatment if they had the highest risk of PML, compared to 24% patients with the second-highest PML risk [55]. No patient discontinued the treatment post-intervention in the lower risk groups [55].

In summary, the studies in the present review show a trend towards a critical attitude towards their DMD post-intervention with some discontinuation due to these attitudes, although the impact on patients' decisions was generally inconclusive in the long-term.

3.3.6. Intervention feedback

MS patients in **six** studies provided feedback on the interventions using self-report measures. Relative to the control group, MS patients in the intervention group felt better informed and felt that important questions had been adequately answered even after six months following intervention [41]. Similarly, MS patients deemed the intervention they received as important and felt that this did not increase worries [50]. In fact, 84% of MS patients stated that they would recommend the intervention to other patients

[50]. Majority of patients reported the intervention as useful, and were particularly satisfied with specific training they received during the intervention [51]. Likewise, there was a significant increase in patients perception of being informed, in addition to the feeling of certainty and confidence of being able to handle all treatments following a DMD information intervention [52]. Over 80% of MS patients trialling an informational website reported that the website was easy to navigate, easy to understand and was useful [54]. Following informational materials explaining confidence intervals, patients in the intervention group consistently rated the information as being understandable, relevant and beneficial [44].

Despite the diversity of the DMD interventions employed in these **six** studies, self-report measures indicate that patients generally perceive any type of interventions as favourable in facilitating understanding of DMD information.

4. Discussion and conclusion

4.1. Discussion

The present systematic review evaluated **15** interventions designed to improve MS patients' ability to understand complex risk-benefit profiles of DMDs. Studies in the review included MS patients with different clinical subtypes and those taking a variety of DMDs. Studies employed a range of outcome measures and not all studies included baseline data or control group. Some studies had methodologies that precluded firm conclusions.

Interventions within the present review provided treatment information using booklets, websites, vignettes and education programmes. Half of the interventions included some form of interactive component [41,42,45,47,48,51,52]. Yet, there was no apparent advantage of interactive versus passive interventions on understanding. There was also no apparent benefit of longer and multicomponent interventions in comparison to shorter and basic interventions such as leaflets in the current review. From this, it can be presumed that interventions which are easier to administer and require fewer resources may be just as beneficial to employ as longer interventions. Moreover, less than half of the interventions manipulated or explained the formats used to present treatment information, such as framing, numerical formats or graphical formats [41,43,44,50,53,54]. This is surprising considering that presentation formats are a key criteria for an effective evidence-based educational intervention [18] and can significantly impact understanding of treatment information [25,26,28,34,35]. Therefore, the use of presentation formats should be carefully considered when designing an educational intervention.

In general, it was difficult to make comparisons between these interventions since they were very diverse in their content and administration. In particular, it was not possible to draw conclusions about the most effective intervention which could improve understanding of DMD information in MS patients.

However studies that recorded patient's feedback of the interventions all received favourable reviews [41,44,50–52,54], which indicates that any form of intervention providing DMD information beyond routine health-care are generally well-accepted by MS patients.

In terms of the impact of interventions, four interventions improved understanding of overall information provided during intervention, despite using very different interventions and study designs [44,45,47,52]. For treatment risk knowledge specifically, MS patients initially showed an underestimation of treatment risks during routine healthcare, but showed greater understanding of both real and hypothetical treatment risks post-intervention. This improvement in risk understanding seemed related to multicomponent interventions [42,48], information which was easier to understand [43,50,54] and when personal risk attribution was perceived as low [43]. However, it was not possible to determine the extent to which these interventions were able to improve understanding of both adverse risks and side-effects that are less severe but commonly associated with DMDs. Nevertheless, interventions designed to improve understanding of treatment risks could be very beneficial for patients making treatment decisions, since even very small changes in the risks of DMDs can have a huge impact on treatment choice [56,57]. In fact, some studies in the present review showed a trend towards patients becoming critical or discontinuing treatment when risks were better understood [41,43,46,55]. This suggests that patients are likely to review decisions for their current DMD following new and enhanced understanding of treatment risks. Considering this, it is important that patients perceive information accurately about DMD risks when making initial treatment decisions, so that the true risks associated with their chosen treatment are in line with patients' preferences. Although, some studies in the review showed that despite greater understanding of treatments risks, MS patients seemed to underestimate their personal chance of developing these risks [46,50]. Interventions in the future could therefore attempt to converge personal risk attribution with accurate understanding of treatment risks, to ensure patients are able to apply the knowledge they gain from the intervention and make informed treatment decisions based on personal preferences.

Improvements in understanding the benefits of treatments were less pronounced. Objectively, many patients did not understand or tended to overestimate the benefits of taking their treatment, even after receiving additional information [43,46,49,53]. This can be problematic for selecting a course of treatment, as patients are more likely to prematurely discontinue treatment if DMD benefits are perceived as higher than actual benefits [49,58]. Such poor adherence to DMDs can have both direct and indirect costs for MS patients [59]. However, patients did not significantly change their treatment decisions following intervention, similar to the review by Köpke and colleagues [36], it is difficult to determine the effects of accurate understanding of treatment information on treatment adherence and shared treatment decision-making. This affirms that understanding of treatment information is simply a precursor to effective shared decision-making and other key factors such as patient autonomy, patient preferences or decision regret, would also need to be addressed in interventions to directly improve shared treatment decision-making [15,60–62]. Such interventions or decision aids were present in only three of the 15 included studies in the current review [41,42,48].

Additional factors which can likely influence patient's understanding of DMD information were not fully explored by interventions in the present review. Patients' numeracy and literacy skills have the ability to modify understanding of the risks and benefits of treatments, with lower skills often leading to larger number of errors [63–65]. This was only explored in one

study within the present review, where patients unable to interpret numerical data demonstrated the least accuracy in understanding the treatment risk information even after intervention [50]. Aspects of cognitive functions affected by MS itself are also likely to influence patient understanding, including: verbal and visual-spatial memory [8,66], information-processing speed [5] and decision-making [67,68]. Yet only one interventional study monitored cognitive impairments of MS patients in the current review [45]. This study showed that fictitious treatment understanding in MS patients with cognitive impairments was considerably lower compared to MS patients who do not present these symptoms. However, following additional cueing during intervention, the same level of understanding and recall was shown in cognitively impaired MS patients compared with cognitively intact MS patients [45]. Hence, future interventions providing treatment information to MS patients may benefit from ensuring that patients of all abilities, and those presenting cognitive impairments due to MS, are able to benefit from the additional information given beyond routine healthcare.

A limitation of the present systematic review was the difficulty in drawing robust conclusions or conducting a meta-analysis for the efficacy of interventions as a result of the different outcome measures employed. A narrative synthesis was considered to be the most appropriate format for reviewing the studies. It is important to acknowledge that such a qualitative review is subject to greater analysis bias than a quantitative systematic review.

4.2. Conclusion

The present review was an inclusive attempt to compare different types of interventions which provide treatment information beyond routine healthcare, while evaluating their efficacy on understanding of treatment risks and benefits. Despite the heterogeneous findings, it is conceivable to conclude that interventions providing treatment information beyond routine healthcare are preferred by MS patients and have the potential to improve understanding of overall treatment information, particularly treatment risks. Understanding of treatment benefits do not seem to be reliably improved by the reviewed interventions. There was no conclusive effect of interventions on MS patients' decisions for DMDs. No particular intervention type emerged as reliably efficacious. Interventions that were longer and comprehensive performed similar to shorter interventions requiring fewer resources. There is a need for a standardised information-based tool which can draw on the strengths of currently available interventions and which can improve understanding of both the risks and benefits of treatments.

4.3. Practice implications

The implication from this review is that MS patients appreciate interventions which provide information about the risks and benefits of DMDs beyond routine healthcare. Future interventions need to ensure that effective presentation methods are employed to optimise understanding of DMD information during decision-making, and that MS patients of all abilities and those presenting cognitive impairments can also benefit from the additional support.

Conflict of interest

GR has no disclosures.

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