

The effect of spaced presentation of treatment information on recall and
understanding of risk relating to medication in Multiple Sclerosis

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June, 2015

Submitted in partial fulfilment of the requirements for the degree of Doctor in Clinical
Psychology (DClinPsy), Royal Holloway, University of London.

Acknowledgements

Foremost, I would like to express my sincere gratitude to Professor Dawn Langdon who provided valuable guidance and encouragement throughout the entire research process. Thank you also to Dr. Samantha Altendorff whose assistance with recruitment, as well as many helpful insights at all stages of this project, is greatly appreciated. I would also like to acknowledge the contributions of Dr. Diane Playford and the entire Multiple Sclerosis Centre team at the National Hospital for Neurology and Neurosurgery (NHNN), in particular Margaret Vincent and Bernadette Porter. A special thank you to each participant without whom this research would not have been possible. Their cooperation and enthusiasm for the study was exceptional.

To my parents, Anne and Seán, I cannot thank you enough for your constant support, encouragement and wisdom throughout this research process and through all the years of my education. Thank you also to my sister, Patricia, and brother, Conor, who I can always depend on, and to Henry for your positivity and support throughout the past three years and more.

Abstract

Recent developments of more effective Multiple Sclerosis (MS) medications with severe side-effect profiles mean that patients with MS must recall and comprehend highly complex risk-benefit treatment information. Yet studies have shown reduced risk awareness in people with MS, which may be associated with MS-related cognitive impairments (e.g. reduced information-processing speed and learning). Spaced presentation, whereby information is presented over time and interspersed with breaks, can improve recall in patients with MS on simple paragraph and name-learning tasks. However the benefits of spaced presentation in patients with MS have not been explored for more complex, clinically-relevant information. The present study explored whether spaced presentation of treatment-related risk information leads to improved recall and understanding in patients with MS (n=30) and healthy controls (n=30). Participants heard information about fictitious drugs presented in three formats: with gaps (spaced condition), continuously (massed condition), and continuously followed by a 10-minute delay (massed-with-delay condition). Immediate recall and understanding was assessed. They also completed neuropsychological tests. Mixed design ANOVAs showed a main effect of group, with MS participants performing significantly worse than controls for both immediate recall and understanding of treatment-related risk information. There was also a main effect of presentation format for immediate recall. Participants recalled significantly more information in the spaced relative to both massed and massed-with-delay conditions and in the massed relative to the massed-with-delay condition. Cognitive deficits correlated with recall and comprehension in the MS group. This study provides initial support for the benefit of spacing for recall of risk information in MS.

However, spaced presentation did not aid comprehension of treatment-related risk information in either group. The breaks in information presentation may ameliorate effects of reduced processing speed on recall. However, the complexity of comprehending medication risk information may be too great a challenge for a spacing intervention to overcome in the context of MS-related cognitive impairment. Clinical implications are discussed.

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1. Introduction

1.1. Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic progressive neurological disorder of uncertain aetiology which affects the brain and spinal cord. It is typically diagnosed in early-middle adulthood (20-40 years) and affects approximately 2.5 million people worldwide (Kingwell et al., 2013; Markowitz, 2013).

1.1.1. Pathophysiology of MS

The underlying cause of MS is complex, multifactorial and not yet fully understood but is thought to result from a combination of genetic predisposition and environmental triggers (Compston & Coles, 2008; Hauser & Oksenberg, 2006). The pathological processes involved in the development and progression of MS are better understood (Compston & Coles, 2008). It is generally accepted that MS development involves two primary distinct processes: (i) *inflammation* and (ii) *neuro-degeneration*.

During *inflammation*, the myelin sheath – a protective, insulating area surrounding the axons of nerve cells which aids fast communication between nerve cells – becomes damaged, causing demyelination (Compston & Coles, 2008). In earlier stages of MS, remyelination can occur, thus restoring communicative function. However, repeated inflammation causes plaques, called lesions, to build up in the brain and spinal cord (Compston & Coles, 2008; Hauser & Oksenberg, 2006).

Over time, demyelination leads to *neuron and axonal degeneration* or cell death (Compton & Coles, 2008; Hauser & Oksenberg, 2006). As the disease progresses and new lesions develop, axon and neuronal degeneration becomes more

widespread, resulting in permanent neurological disability (Tallantyre et al., 2010).

MS involves both white matter (composed of axons which aid communication between grey matter and other areas of the body) and grey matter (composed of nerve cells which receive information from and generate information to the rest of the body) pathology, with grey matter areas impacted more severely as the disease progresses (Calabrese, Filippi, & Gallo, 2010).

1.1.2. Symptoms, Diagnosis and Clinical Course

Inflammation, demyelination and neuronal degeneration in the central nervous system (CNS) lead to a wide range of potential symptoms which vary substantially between people with MS. The heterogeneity of MS symptom profiles and clinical course depends in part on the specific lesion sites within the brain (Compton & Coles, 2008). Typical symptoms include motor, visual or other sensory difficulties. Cognitive functions are also frequently impacted (Hauser & Oksenberg, 2006). Fatigue is one of the most commonly reported and disabling symptoms affecting up to 90% of the MS population (Bol, Duits, & Hupperts, Vlaeyen, & Verhey, 2009). Depression is also common, affecting about 50% of people with MS (Arnett & Strober, 2011). As the disease progresses, these physical, cognitive and psychological symptoms can become more frequent and severe leading to an increased level of disability and reduced quality of life, impacting on an individual's capacity to engage in work, leisure activities and social relationships (Fernandez-Jimenez & Arnett, 2014; Hoogs, Kaur, Smerbeck, Weinstock-Guttman, & Benedict, 2011; Janardhan & Bakshi, 2002).

A clinical diagnosis of MS is typically established in accordance with the McDonald criteria (McDonald et al., 2001) based on the presence of lesions within

the CNS and two or more discrete episodes of neurological dysfunction (Polman et al., 2005).

1.1.3. MS Subtypes

MS is classified into 4 clinical sub-types: (i) relapsing-remitting, (ii) primary progressive, (iii) secondary progressive and (iv) progressive relapsing MS, each characterised by different presentations.

- (i) Approximately 85% of people with MS initially present with relapsing-remitting MS (RRMS). These patients experience alternating episodes of neurological disability followed by subsequent periods of recovery and remission, with this interchange lasting between 3-25 years (Confavreux & Vukusic, 2004; Hurwitz, 2009).
- (ii) Approximately 90% of patients with RRMS ultimately develop secondary progressive MS (SPMS). This sub-type is characterised by continuous, permanent neurological decline (Hurwitz, 2009).
- (iii) 10-15% of people with MS receive an initial diagnosis of primary progressive MS (PPMS). This involves continuous, progressive neurological decline with no remission phases and typically has a later age of onset relative to RRMS (Confavreux & Vukusic, 2004; Hurwitz, 2009).
- (iv) Progressive-relapsing MS (PRMS) is a disease course experienced by about 5% of people with MS and is characterised by progressive neurological decline as well as acute episodes of relapse with or without remission (Hurwitz, 2009).

1.1.4. Section Summary

MS is a chronic progressive neurological disease affecting the brain and spinal cord (CNS). Inflammation and demyelination cause lesions to develop in sites within the CNS, eventually leading to neurodegeneration. This results in a range of visual, motor, sensory, cognitive and psychological symptoms which lead to increased disability and reduced quality of life as the disease progresses. In the majority of cases (85%), patients initially experience alternating episodes of relapse and remission which ultimately develops into progressive neurological decline. There is no known cure for MS. Instead, treatments centre on disease-modifying medications which help to slow progression of the disease and associated disability.

1.2. Drug Treatment for MS

There are a number of medications which slow progression of the disease and delay development of further lesions thus slowing the progression of neurological disability. Consequently, they are known as disease-modifying treatments (DMTs). These medications are typically divided into two categories: first-line and second-line treatments. There is no gold standard DMT for people with MS, thus treatment decisions are a complex, multi-faceted matter which must be made at an individual level (Lugaresi et al., 2013).

1.2.1. Current Status: First Line versus Second Line Disease Modifying Treatments (DMTs)

First-line medications refer to those drugs for which the balance between the known risks and benefits ratio is largely positive. These drugs are deemed efficacious, safe

and well-tolerated (Ontaneda & Di Capua, 2012). Generally, potential side-effects are considered to be minor or ‘acceptable’ but are not life-threatening (Marrie & Rudick, 2006; Miller, Spada, Beerkircher, & Kreitman, 2008). Their safety profile has been consistent for a number of years, up to 20 years in the case of Beta Interferon and Glatiramer acetate (Miller et al., 2008; Ontaneda & Di Capua, 2012). Unfortunately, these first-line DMTs are not effective for a relatively large proportion of patients (Ontaneda & Di Capua, 2012).

In contrast, the more recently developed second-line MS medications are typically more effective than first-line medications. Yet second-line medications also possess severe, potentially life-threatening side effects. Limited medication trials mean that their long-term side effects and safety record remains unclear (Lugaresi, 2013). Given the disparate efficacy and risk profiles of first- and second-line medications, patients with MS face a complex decision-making process in which the pros and cons of each treatment option must be carefully considered.

1.2.2. Mechanism of Action of DMTs and Potential Effects on Cognition

All DMTs are classified as immunotherapies. It is thought that they work by regulating the immune system, suppressing the inflammation-inducing T-cells (i.e. cells which cause inflammation in the CNS) which the body’s immune system has failed to regulate (Compton & Coles, 2008). However, the specific mechanism of action of DMTs in MS is not very well understood. This is particularly true for first-line medications. Beta Interferon, a first-line medication, is a protein which is thought to inhibit the uptake of a chemical which can activate T-cells. Therefore, Beta Interferon may work by reducing the level of inflammation, leading to reduced

neuronal and axonal degeneration and thus slower progression of disability (Kieseier, 2011).

The mechanism of action of newer, second-line DMTs is more well-defined. These also act by reducing inflammation which then decreases the rate of lesion development in the CNS. However, the method of doing so is different. Second-line DMTs reduce inflammation by binding to T-cells, inhibiting them, and so the T-cells are then unable to trigger the process of inflammation of cells in the CNS (Hoepner et al., 2014). These second-line medications may also interrupt inflammation that has already begun in the CNS (Hutchinson, 2007).

A very limited number of studies have explored the effect of DMTs on cognitive function in MS (Benedict & Zivadinov, 2011) and thus the effect of most DMTs on cognitive function remains uncertain. One recent study explored the benefits of Natalizumab for cognitive function and fatigue in MS. Following a 1-year treatment period, a significant decrease was observed in the number of MS participants who were classified as cognitively impaired, although further improvement in the second year was not statistically significant (Iaffaldano et al., 2012). A significant decrease in fatigue was also reported which may or may not have secondary effects in terms of improving cognitive function (e.g. Bailey, Channon, & Beaumont, 2007; Krupp & Elkins, 2000). Another more recent study reported significant improvements in information-processing speed and attention in MS following Natalizumab treatment over a 2-year period (Kunkel et al., 2015). It has been hypothesised that DMTs may improve cognitive function or slow cognitive decline by slowing the development of new lesions in areas responsible for various

cognitive functions (Kunkel et al., 2015), particularly where cortical, gray matter, lesions are prevented (Papadopoulou et al., 2013).

1.2.3. Dangers Associated with DMTs

In order to further comprehend the complexity of the decisions to be made regarding MS treatments, two common second-line DMTs are discussed: Mitoxantrone and Natalizumab.

1.2.3.1. Mitoxantrone

Mitoxantrone, is a second-line MS medication which is approved for the treatment of PRMS, SPMS and aggressive RRMS (i.e. a rare, rapidly evolving form of RRMS involving more than two relapses in a year and associated with rapid progression of disability), typically where patients have not responded or have partially responded to first-line medications (Lugaresi et al., 2013). It has been shown to be highly effective in reducing relapse rate and disability progression (Martinelli, Radaelli, Straffi, Rodegher, & Comi, 2009), particularly in the case of RRMS (Esposito et al., 2010), with long-term benefits following discontinuation (Marriott, Miyasaki, Gronseth, & O'Connor, 2010). However, like Natalizumab, Mitoxantrone's high efficacy needs to be evaluated along with its serious potential side-effects including cardiotoxicity such as systolic dysfunction (12%) or congestive heart failure (0.2-0.5%) (Marriott et al., 2010; Martinelli et al., 2009) as well as therapy-related acute myeloid leukaemia (TRAL; between 0.25-0.93%) (Chan & Lo-coco, 2013; Marriott et al., 2010).

1.2.3.2. Natalizumab

Natalizumab was initially approved as a second-line treatment for RRMS in the European Union in 2006 but with specific safety restrictions due to a number of prior fatalities (Hoepner, Faissner, Salmen, Gold, & Chan, 2014). The European Medicines Agency (EMA) specifies that Natalizumab may only be prescribed to patients with RRMS who have high disease activity and who have not responded to first-line medications, typically Beta Interferon or Glatiramer acetate, as well as to newly-diagnosed individuals with severe, rapidly advancing relapses. It may only be prescribed as a monotherapy and not in conjunction with other MS therapies (Hopener et al., 2014; Lugaresi et al., 2013).

Natalizumab is a highly effective treatment for MS. Patients taking Natalizumab benefitted from a greater reduction in relapse rate and disability progression as well as reduced lesion activity and brain atrophy on MRI scans (Lanzillo et al., 2011; Spelman et al., 2015) when compared to patients who were prescribed first-line medications such as Beta Interferon therapy. Positive effects on quality of life, cognition, fatigue and mood have also been reported (Hoepner et al., 2014).

Importantly however, Natalizumab also comes with the risk of Progressive Multifocal Leukoencephalopathy (PML), a life-threatening virus of the CNS which typically results in moderate to severe disability in survivors (Sorensen et al., 2012). The risk of PML in patients with MS who are on Natalizumab is estimated to be between 0.09 cases per 1000 patients and 10.6 per 1000 patients (Lugaresi et al., 2013) depending on a number of known risk factors. The risk of PML on Natalizumab

provides a particularly good example of the complexity of information which patients with MS must comprehend before making a decision regarding their treatment.

Specifically, there are three primary risk factors known to substantially increase one's chance of developing PML while on Natalizumab: testing positive for the presence of anti-JC virus antibodies in the blood, previous or current immunosuppressant use, and treatment duration (Sorenson et al., 2012). An individual's risk of developing PML depends on the number of these risk factors present, and this can change over time. For example, patients can change from a negative to a positive anti-JC virus antibody status (Lugaresi et al., 2013). Natalizumab treatment lasting over two years, as well as higher dosages, further increases the risk of PML (Sorenson et al., 2012). A risk-factor algorithm is used to interpret an individual's relative risk of developing PML based on these three primary risk factors (Sorenson et al., 2012). Evidently then, the volume of medical and statistical information one must consider when evaluating risk of PML is vast and complex.

1.2.4. Complexity of Treatment-related Patient Information

The risk of PML on Natalizumab described above provides a particularly good example of the complexity of medical and statistical information which patients must master before being able to make a well-informed decision regarding their treatment. The above descriptions of both Mitoxantrone and Natalizumab also elucidates the complicated nature of MS-related treatment decisions - evaluation of risk-benefit profiles for each treatment option is essential and must be considered in the context of an individual's disease severity and progression, medical history, response to previous

DMTs, preferences and quality of life (Lugaresi et al., 2013). In the case of Natalizumab and Mitoxatrone as well as other second-line MS treatments, patients must balance the higher efficacy rates with complicated risk information. With the continued advancement of newer, stronger MS medications (Lugaresi et al, 2013), this ability to consider many competing risk-benefit ratios will become more crucial.

It should also be clear from the above accounts that the types of statistical risk information regarding treatments which patients with MS encounter is varied and complex, further complicating the processes of comprehending treatment-related risk information. Patients may receive statistical risk information which is portrayed in percentages (e.g. 80% effective), frequencies (e.g. 1 in 70 patients), odds (e.g. 30 to 1), number needed to treat (e.g. 50 people need to be treated with this medication for 1 person to experience a reduction in relapse rate) or classic probabilities (e.g. 0-1) (Lipkus, 2007). Furthermore, this information may only be presented in one numerical format, which impacts cross-examination. This is known to impede accurate understanding of risk information (Lipkus, 2007). The issue of numerical information and its role in risk awareness in people with MS is discussed further in subsequent sections (see section 1.3.).

1.2.5. Section Summary

MS treatments are divided into two categories based on their known efficacy, safety and risk profiles, namely first-line and second-line medications. Both have been shown to slow disease and disability progression. Currently, second-line medications are only licensed for patients on first-line medication with objective evidence of breakthrough disease. Unfortunately however, these more efficacious drugs also carry

the risk of severe, life-threatening side effects. Consequentially, patients must encode, comprehend and recall complex risk information for each treatment option which is often presented in high-level numerical and statistical formats. As the development of second-line medications progresses, patients will continue to encounter situations in which they must choose between more or less efficacious medications with mild to potentially life-threatening side effects. Ultimately, a shared decision-making process occurs between the physician and patient. They jointly critically evaluate the risk-benefit profiles of each treatment option in the context of that individual's MS profile, medical history, personal values, preferences and quality of life.

1.3. Shared Decision-Making and Evidence-Based Patient Information:

1.3.1. Shared Decision-Making Summary

Shared decision-making (SDM) refers to a model of patient-clinician communication which promotes an active role for patients and an equal balance of power and responsibility in relation to decisions about medical care. The central premise underlying a SDM model is that patients' preferences and values should be explored and factored into the final treatment decision (Elwyn et al., 2012). This is in contrast to more traditional clinical practice where the 'clinician as expert' ideology prevailed and clinicians felt able to make decisions for the patient. Balanced information-sharing by clinicians, for all possible treatment options, is key, particularly in the case of chronic or life-threatening illness for which there are a number of potential treatments with some degree of uncertainty (Charles, Gafni & Whelan, 1997). The overall aim is to provide patients with greater autonomy and confidence to make more informed, balanced choices regarding their care.

Several different models of how best to implement SDM in practice have been put forward. Elwyn and colleagues (2012) developed one such model containing three steps: Firstly, clinicians should *introduce choice*, making sure the patient is aware that multiple possible treatment options exist; secondly clinicians should *describe each treatment option* in sufficient detail and in a way that is accessible to the patient; finally, clinicians should *facilitate an exploration of patients' preferences* before engaging in joint *deliberation* which includes processes such as jointly weighing up pros and cons and considering consequences of each option. Ultimately these three steps lead to a compromise where an *informed joint decision* regarding treatment is reached (Elwyn et al., 2012).

Given the chronic nature of MS and its diverse range of treatment options, some of which have limited efficacy, severe potential side-effects, or uncertain outcomes, SDM has been strongly advocated in MS health settings (Veloso, 2013; NICE, 2003). However, a commonly cited challenge for SDM is the measurement of patient decision-readiness, particularly their level of risk awareness, with few standardised measures available (Department of Health, 2012). This is especially pertinent given the frequency of MS-related cognitive impairments and their association with understanding of treatment information, reasoning and expression of treatment choice (e.g. Basso et al., 2010; McKnight, 2007). Before describing the evidence for specific MS-related cognitive impairments and their impact on risk awareness, it is worth reviewing the current evidence for reduced risk awareness in both the general population and MS population. For the purpose of this study, risk awareness is operationalised as the understanding and recall of risk information.

1.3.2. Evidence-Based Patient Information (EBPI)

Evidence-based patient information (EBPI) has been deemed a necessary ‘pre-requisite’ for SDM (Heesen et al., 2010). EBPI comprises the medical information on all available treatment options. It should be accessible, reliable and comprehensive and presented in a way that facilitates patient understanding. However, provision of accessible EPBI in practice can be challenging. Firstly, individuals have been shown to vary greatly in their abilities to comprehend health-related risk information, particularly health numeracy (Peters, 2012; Reyna, Nelson, Han, & Dieckmann, 2009) and, secondly, consensus on the most appropriate presentation format is lacking (Peters, Hibbard, Slovic, & Dieckmann, 2007; Reyna et al., 2009).

The NICE guidelines for the management of MS in primary and secondary care settings stipulate that clinicians should provide patients with oral and written EBPI at the time of diagnosis, including information on DMTs, and a face-to-face follow-up appointment should be offered within 6 weeks of this diagnosis (NICE, 2003). The Association of British Neurologists’ guidelines for prescribing medication to people with MS state that “patients should be fully informed of relevant facts and uncertainties before making a decision in discussion with their treating neurologist” (ABN, 2009). It is evident then, that patients should be informed about all the benefits and risks of different treatment options. Furthermore, Pietrolongo and colleagues (2013) found that increased clinician time, increased facilitation of patient involvement by clinicians, and greater attendance by clinicians to patient preferences for delivery of information all correlated with better observer ratings of patient involvement and satisfactory shared decision-making in initial MS clinical consultations.

However, there is no entirely standardised way of presenting information in MS clinical consultations in terms of the extent of information provided on each DMT, the provision of additional material such as information sheets, the number of sessions in which DMT information is discussed, or the communication style of clinicians which may range from directive to interactive and may vary greatly across clinicians (e.g. Pietrolongo et al., 2013; Robinson, 2002). For example, provision of verbal and written information (i.e. a NICE-recommended information pack specifically for newly diagnosed patients with MS) on DMTs is typically offered in MS clinics in a one-off rather than a staged process. However, in the case of Natalizumab, a more staged process of decision-making is typical given the risk of PML. In this case, oral and written EBPI on the risks and benefits of this medication is initially provided. Later patients are screened for the presence of the JC virus antibody and, following this, a risk algorithm is drawn up which provides them with more personalised risk estimate for PML. Patients then have some time to decide on their willingness to take this risk (Lugaresi et al., 2013).

1.3.3. Limitations on the Understanding of Health-Related Risk Information in the General Public

The primary challenge encountered by clinicians in implementing SDM, even where comprehensive EBPI has been provided to individuals, is low numeracy (Elwyn et al., 2012). Numeracy is typically defined as the ability to accurately comprehend mathematical concepts and probabilistic information (Peters, 2012).

Studies consistently demonstrate that the general public are poor at understanding information about health risks including risk-benefit ratios,

probabilistic information related to medical treatments, and perceptions of the likelihood of a risk occurring (Reyna et al., 2009). This is true even for some highly-educated individuals (Lipkus, Samsa, & Rimer, 2001). The most recent nationwide survey of numeracy skills revealed that just 51% of England's working-age adult population had 'good numeracy', defined as GCSE-level (grades D-G) or above, while 49% (17 million adults) had 'poor' numeracy, functioning at the level expected for schoolchildren aged 5-11 years (DfBIS, 2012).

A number of tendencies which contribute to the poor perception of numerical risk information have been observed. Individuals tend to assume that risks decrease as benefits increase and vice versa. However, rather than an inverse relationship, risk-benefit relationships are often positive (Alhakami & Slovic, 1994). Indeed this is typically the case with newer, second-line MS medications where both the potential benefits and risks are increased.

Furthermore, the general public frequently exhibit difficulties in understanding interactions between two risk factors, with people typically underestimating the magnitude of the combined risk of two or more risk factors (Reyna et al., 2009).

In a somewhat similar vein, individuals are generally poor at understanding cumulative risk, typically making underestimations (e.g. Knauper, Kornik, Atkinson, Guberman, & Avdin, 2005), although overestimations have also been documented (e.g. Fuller, Dudley & Blacktop, 2004). Again, with many second-line MS medications, risk has been shown to increase over time. For example, risk of developing PML while taking Natalizumab increases significantly after two years of treatment (Sorenson et al., 2012).

Finally, it has frequently been demonstrated that the general public have difficulties in correctly interpreting small risk probabilities, particularly those below 1%, with the risk either over-estimated, under-estimated or simply disregarded completely (Lipkus, 2007).

Peters (2012) and others have argued that the issue goes further than numeracy comprehension. Affect and psychological factors such as framing effects may also limit many people's interpretation of numerical risk information. The effect to which an individual is influenced by these non-numerical factors is associated with their level of numeracy (high or low). For example, those with lower numeracy skills are more likely to perceive risk as higher when it is framed in negative terms (e.g. 27% will develop heart problems) and lower when framed in positive terms (73% will not develop heart problems), whereas people with high numeracy judge the risk as similar regardless of how the information is framed.

For those with lower numeracy, positive or negative mood state at the time risk information is presented is more likely to result in low-risk likelihood or high risk-likelihood perceptions respectively (Petrova, van der Pligt, & Garcia-Retamero, 2014). Furthermore, individuals can be influenced by feelings even when provided with an overt indication that two risks are equally likely. One study asked participants to imagine they had been successfully treated for a particular cancer (e.g. Thyroid cancer) and then informed participants that they had an equal risk of later developing either recurring Thyroid cancer or a new cancer type (Skin cancer). However, participants reported experiencing higher levels of worry about developing the recurring cancer relative to the new cancer type and a substantial number of

participants (44%) consequently reported *feeling* as if the recurrent cancer was more likely to develop (Zikmund-Fisher, Fagerlin, & Ubel, 2010).

Despite the limitations with numerical communication of risk, it is largely felt to be more appropriate than verbal communication of risk. Verbal descriptions of risk (e.g. 'likely', 'unlikely', 'rare', 'possible') can lead to greater misinterpretation due to the wider range of different meanings which individuals may conclude (Lipkus, 2007). For instance, one person may deem a risk of 55% as likely whereas another may deem 75% as likely. Consequently, achieving uniformity of understanding across individuals and contexts using verbal risk information appears more challenging than doing so with numerical information.

1.3.4. Limitations on the Understanding of Health-Related Risk Information in Non-MS Patients

Existence of a current health condition and subsequently greater exposure to treatment information does not appear to improve risk awareness (i.e. understanding and recall of risk information). Individuals with Type II Diabetes have an increased risk of developing serious Diabetes-related diseases such as cardiovascular disease. Yet, such individuals typically underestimate their risk of developing these conditions which in turn influences their decisions about lifestyle choices and medication adherence (e.g. Saver, Mazor, Hargraves, & Hayes, 2014).

In another study, a majority of prostate cancer patients held misconceptions about the risks and benefits of treatments, with their treatment decisions being influenced more by affect (e.g. fear, anxiety) rather than accurate risk information (Denberg, Melhado, & Steiner, 2006). Survivors of breast cancer have been shown to

largely misperceive the risk of cancer recurrence. This may be an overestimate or underestimate with both level of anxiety (Kelly et al., 2013) and lower health numeracy (Kelly, Shedlosky-Shoemaker, Porter, DeSimone, & Andrykowski, 2011) fuelling these misperceptions.

1.3.5. Reduced Health-Related Risk Awareness in MS

Findings of reduced risk awareness in people with MS are also common. Using a self-report measure, one study revealed that in the MS population overall level of MS-related risk knowledge was low (Heesen, Kasper, Segal, Kopke, & Muhlhauser, 2004), while another found that patients with MS overestimated the 2-year and 10-year risks of becoming wheel-chair dependent but underestimated the lifetime risk (Janssens et al., 2003).

Other studies have focused on risk awareness specifically in relation to treatment decisions. Using a self-report questionnaire, one study measured knowledge and risk perceptions about the side effects of Mitoxantrone in people with MS. They revealed that 58% underestimated the risk of Leukaemia while 82% underestimated the risk of cardiotoxicity (Hoffman et al., 2012). Another study revealed that people with MS were more likely than practitioners to overestimate the benefits of the second-line treatment Natalizumab (Heesen et al., 2010a).

A recent examination of health literacy in people with MS concluded that the majority of participants (65.5%) performed well on two health literacy measurements (Medical Term Recognition Test (METER) & Newest Vital Sign (NVS)) and were deemed to have 'functional health literacy' (Marrie, Salter, Tyry, Fox, & Cutter,

2014). Yet a substantial number, 34.5%, did not reach this functional level on both measures.

Evidently then, there is a need for greater provision of EBPI in MS clinical settings. An increased amount of quality information may facilitate greater risk awareness in the MS population. Indeed, patients with MS appear to agree. Numerous studies demonstrate a desire among patients with MS for greater information provision regarding treatment options (e.g. Heesen et al., 2004; Kasper, Kopke, Muhlhauser, & Heesen, 2006). Some studies have begun to explore the benefits of EBPI within MS.

1.3.6. Evidence-Based Patient Information as a Means of Improving Risk Awareness in MS

Numerous studies over the past decade have consistently shown that provision of EBPI at MS diagnosis significantly improves risk awareness regarding treatment in this population (e.g. Heesen, Solari, Giordano, Kasper, & Kopke, 2010b; Kasper et al., 2006). One study developed an information aid for newly diagnosed patients with MS which consisted of a personal interview with a physician, an information booklet and navigable compact disc. The information aid significantly improved MS knowledge relative to current clinical practice (diagnosis disclosure alone), evidenced by higher scores on the MS Knowledge Questionnaire (MSKQ) (Solari et al., 2010).

Another study found that treatment-related risk awareness in patients taking the second-line medication Mitoxantrone was increased after reading an EPBI information brochure. Specifically, they demonstrated a greater understanding of the risk of developing Leukaemia while on Mitoxantrone, with the number of patients

correctly estimating the risk rising significantly from 40% pre-EBPI intervention to 82% post-EBPI intervention. They also demonstrated a significant increase in estimating the risk of developing cardiotoxicity, with accurate risk awareness rising from just 16% to almost 50% following the provision of EBPI. However, a tendency to underestimate the risk of potential side effects associated with Mitoxantrone persisted in 18% and 50% of the sample when estimating the risk of leukaemia and cardiotoxicity respectively (Hofmann et al., 2012).

This replicated the findings of an earlier study which also measured the efficacy of an EBPI intervention in the form of an information brochure. In this study, reading of the brochure led to a significant increase in ‘adequate’ risk awareness from 21% to 41%, yet again, a vast number of patients with MS continued to demonstrate ‘inadequate’ understanding of risk (Kasper et al., 2006). EBPI-based education groups have been another method of significantly improving risk knowledge in people with MS (Heesen et al., 2010b).

EBPI is evidently one way to address poor risk awareness in MS. However, provision of the right information is often not sufficient, as was the case in all three of the studies presented above (Hoffman et al., 2012; Kasper et al., 2006; Solari et al., 2010). In all cases, a substantial proportion of the MS sample did not exhibit adequate risk awareness following an EBPI intervention. A greater quantity of information is unlikely to improve risk awareness in those MS patients with low numeracy, MS-related cognitive impairment, or both.

Indeed, specific MS-related cognitive deficits have been documented which further complicate the case of risk awareness in MS and are likely to hamper

attainment of adequate risk awareness in MS over and above any impact of low numeracy. Therefore, further research would benefit from investigating new methods of improving risk awareness in clinical settings, perhaps with a focus on altering presentation format to offset these specific cognitive deficits. Evidence for particular MS-related cognitive deficits and their implications for risk awareness will now be reviewed which should further elucidate the need for more than a simple increase in quantity or quality of EBPI.

1.3.7. Section Summary

A shared decision-making (SDM) model of patient-practitioner communication is strongly advocated in MS health settings. Successful implementation of this model relies on the provision of comprehensive evidence-based patient information (EBPI) that is accessible to patients. EBPI typically comprises numerical and statistical information detailing risks and benefits of health and treatment-related issues. However, a multitude of studies document low numeracy in the general population, non-MS patients and patients with MS, even for some highly-educated individuals. Low numeracy leads to widespread under-estimation and over-estimation of risk probabilities in these populations. This is particularly consequential for the MS population given the continued emergence of newer, stronger MS medications which hold greater benefits but may pose more severe consequences.

While, it has been shown that EBPI can improve risk awareness in some individuals with MS, a substantial percentage continue to misperceive risk. Thus, it is clear that an increase in quality and quantity of information (i.e. EBPI) alone will not lead to an acceptable level of risk awareness in many patients with MS. Moreover,

specific MS-related cognitive deficits likely impact further on risk awareness in a substantial number of patients. Consequently, this author argues for the need to explore new methods of presentation of risk information to facilitate greater risk awareness, ideally by offsetting these specific cognitive deficits. To understand the types of interventions which may facilitate greater risk awareness in people with MS, it is important to understand the nature of MS-related cognitive deficits.

1.4. Neuropsychological Profile of MS:

1.4.1. The Prevalence of Cognitive Impairment in MS

An estimated 40-70% of patients with MS suffer cognitive impairment (Chiaravalloti & DeLuca, 2008; Guimares & Sa, 2012; Langdon, 2011; Sahraian & Etesam, 2014). Cognitive impairment can occur in all MS subtypes and has been documented even at the earliest stages of the disease (Potagas et al., 2008; Shultz, Kopp, Kunkel, & Faiss, 2006) with impairment increasing as the disease progresses (Benedict et al., 2006; Chiaravalloti & DeLuca, 2008). Rather than general cognitive decline, a number of domain-specific deficits consistently emerge including impairments in information-processing speed, memory and new learning, complex attention and executive function (Chiaravalloti & DeLuca, 2008; Drew, Tippett, Starkey, & Isler, 2008; Hoffman, Tittgemeyer & Yves von Cramon, 2007). Functions such as language comprehension, verbal fluency, spatial perception, and simple attention are much less affected (Amato et al., 2012; Clemmons, Fraser, Rosenbaum, Getter, & Johnson, 2004).

1.4.2. Memory and Learning

The ability to learn and later recall new information is often reduced in people with MS. Initial studies attributed this to a difficulty in retrieving information from long-term memory ('retrieval-failure hypothesis') (Rao, Leo, & St. Aubin-Faubert, 1989). However, recent studies point towards poor acquisition of information as the most likely cause ('learning-deficit hypothesis') which then has a secondary effect on retrieval (Lafosse, Mitchell, Corboy, & Filley, 2013). Numerous studies have found that participants with MS required significantly more rehearsals on word-list learning tasks than healthy controls in order to reach criterion but, once at criterion, performed similarly on verbal recall and recognition (e.g. DeLuca, Gaudino, Diamond, Christodolou, & Engel, 1998; Demaree, Gaudino, DeLuca, & Ricker, 2000; Gaudino, Chiaravalloti, DeLuca, & Diamond, 2001; Lafosse et al., 2013). This suggests that verbal memory in MS is impacted by initial learning rather than long-term memory impairment, indicating that memory difficulties in MS are most likely due to poor acquisition rather than poor retrieval.

A recent study was able to quantify memory performance in MS groups. Despite performing significantly worse than controls on acquisition and delayed recall list-learning tasks, memory performance in the MS group was, in clinical terms, in the 'average' range rather than 'impaired' range but was consistently half a standard deviation below the normative mean (Lafosse et al., 2013). This was taken to indicate mild memory impairment in MS, although even mild impairment may impact substantially on patients' lives and treatment-related risk awareness.

1.4.3. Information-Processing Speed

Reduced information-processing speed - the speed and efficiency with which individuals process new information (Chiaravolloti, Stojanovic-Radic, & DeLuca, 2013) - is the most common cognitive deficit in MS. Studies consistently demonstrate that participants with MS produce significantly slower response times than matched controls on a number of well-known tests of information-processing speed including the Stroop test (e.g. Denney, Gallagher, & Lynch, 2011; Lynch, Dickerson, & Denney, 2010), the Paced Auditory Serial Addition Test (PASAT; e.g. Drake et al., 2010; Fisk & Archibald, 2001; Forn, Belenguer, Parcet-Ibars, & Ávila, 2007), the Symbol Digit Modalities Test (SDMT; e.g. Drake et al., 2010) and reaction time (RT) tasks (e.g. Bodling, Denney, & Lynch, 2012; Reicker, Tombaugh, Walker, & Freedman, 2007). Furthermore, the difference in performance between participants with MS and healthy controls on information-processing speed tasks has been shown to increase with increasing cognitive load of a task (e.g. Denney et al., 2011; Paramenter, Shucard, & Shucard, 2007a; Reicker et al., 2007), further emphasising information-processing deficits in MS. Finally, significantly reduced information-processing speed on such a wide variety of tasks as listed above, which also involve a number of other cognitive functions (e.g. working memory, attention, inhibition, planning), further advocates for a generalised deficit in information-processing speed in MS (Denney et al., 2011). More recent studies continue to provide further evidence for this. For instance, processing speed rather than working memory accounted for the majority of the explained variance in performance on a Keeping Track Task for participants with MS (Genova, Legenfelder, Chiaravalloti, Moore, & DeLuca, 2012).

In a longitudinal study, Bergendal and colleagues (2007) demonstrated that these information-processing deficits in MS appear to worsen substantially over time (Bergendal, Fredrickson, & Almkvist, 2007). Interestingly, they also showed that information-processing deficits were the strongest predictor of further cognitive decline in MS. Indeed, the 'Relative Consequence Model' (DeLuca, Chelune, Tulskey, Lengenfelder, & Chiaravalloti, 2004) asserts that reduced information-processing speed is the primary cognitive deficit in MS and underlies other MS-related cognitive dysfunction. This model arose from studies which show that information-processing deficits were significantly more common than working memory (WM) deficits in a large MS sample (e.g. DeLuca et al., 2004). Moreover, on a modified version of the PASAT, participants with MS performed similarly to a control group on WM but required significantly greater processing time, suggesting that information-processing speed is the primary deficit. When task demand increased, requiring greater WM capacity, participants with MS who possessed greater processing speed deficits made more errors. This supports the viewpoint that information-processing speed interacts with WM to cause a secondary difficulty during more complex tasks (Lengenfelder et al., 2006). In relation to new learning, information-processing speed has been shown to be a much stronger predictor of new learning than is WM (Chiaravalloti, Stojanovic-Radic, & DeLuca, 2013), again espousing the Relative Consequence Model.

In summary then, in order for presentation format to influence risk awareness in MS, one must suppose that this format should facilitate increased information-processing speed which would then have positive implications for new learning, later recall and understanding of this information.

1.4.4. Language Comprehension

While acquisition of new information is reduced in MS, likely owing at least in part to reduced information-processing speed, language comprehension appears to be largely intact.

Many studies have employed the Verbal Comprehension Index (VCI) of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III; Wechsler, 1997) to assess language abilities in MS groups. They have found that MS groups typically perform at a level similar to healthy controls on Vocabulary, Information and Similarities subtests, indicating that verbal comprehension and expression, abstract verbal reasoning, and general knowledge are usually preserved (e.g. Clemmons et al., 2004; Drew, et al., 2008; Prakash, Snook, Lewis, Motl, & Kramer, 2008).

In one such study, participants' performance on the WAIS-III was compared with a measure of their pre-morbid intelligence (Wechsler Test of Adult Reading; WTAR) which provided a predicted score for the performance IQ and verbal IQ measures of the WAIS-III. Many patients with MS scored significantly lower than their predicted score on the performance IQ index but relatively few scored significantly lower than expected for verbal IQ (Drew et al., 2008). Performance IQ may be impacted in patients with MS due to visual or motor disturbance associated with the disease. This finding of intact verbal IQ replicates the findings of a previous study which also employed the Verbal Comprehension Index (VCI) subtests of the WAIS-III. Again, they found verbal abilities in people with MS to be largely preserved with patients performing in the average to high-average standardised range

(Clemmons et al., 2004). Overall it was concluded that there is little evidence of a verbal deficit in MS.

Ryan and colleagues (2012) recently conducted the first assessment of neuropsychological performance of participants with MS on the WAIS-IV (Wechsler, 2008), an updated version of the WAIS-III. Again, using this battery, verbal abilities were found to be largely preserved and scores on the VCI were significantly greater than on the Processing Speed Index (PSI) for the MS group (Ryan, Gontkovsky, Kreiner, & Tree, 2012). This suggests that MS impacts less on an individual's verbal comprehension relative to processing speed. However, it should be noted that this study included only those with RRMS. In a sample of patients with RRMS, PPMS and SPMS, it was found that where overall cognitive performance was high, cognitive decline was largely restricted to the domains of perceptual and processing speed. However, where these overall cognitive performance levels were low, all cognitive domains were typically affected, whether perceptual, processing speed, working memory or verbal comprehension (Drew et al., 2008). This suggests that verbal skills may be an additional area of decline in more progressive forms of MS as were included in the current study.

Based on the current evidence, one should expect that verbal abilities will not generally impact on participants' ability to comprehend risk information and, in line with evidence discussed earlier, comprehension is more likely to be impacted by poor numeracy.

1.4.5. Executive Function

Executive function refers to a set of complex, higher-order cognitive processes including inhibition, planning, initiation, working memory (WM) and reasoning (Lezak, 2004). Executive function deficits have been documented in people with MS but have been shown to be less common than other cognitive impairments, most notably information-processing speed and memory deficits (Guimares & Sa, 2012).

There is not yet a definitive account of the aspects of executive dysfunction characteristic to MS, with much variability between individuals (Drew et al., 2008). One study found that participants with MS performed significantly worse than controls on the Wisconsin Card Sorting Test (WCST) and Delis-Kaplan Executive Function System (DKEFS) test, suggesting that MS impacts on one's ability to plan strategically, shift attention, inhibit automatic responses and problem-solve (Parmenter et al., 2007b). Using the DKEFS test battery, Drew et al. (2008) also found some evidence of reduced inhibition and ability to shift attention, working memory and verbal fluency.

There is also some evidence for reduced performance by people with MS on everyday functional tasks which involve executive function. Reduced performance on simple cooking and bill payment tasks was correlated with reduced performance on the Tower of London task, a test that assesses planning and inhibition, in a group of participants with MS (Voebel et al., 2011). People with MS also performed significantly worse than healthy controls on a functional task involving planning and organisation in which they were asked to purchase a return-trip airline ticket using the internet (Goverover, O'Brien, Moore, & DeLuca, 2010).

However, it is acknowledged that an element of executive dysfunction in MS is attributable to slowed information-processing speed, for example timed tests of shifting and inhibition (Drew et al., 2008; Genova, DeLuca, Chiaravalloti, & Wiley, 2013), planning (Denney et al., 2011) or working memory (Legenfelder et al., 2006).

1.4.6. Factors Impacting on Cognitive Function in MS

A number of common symptoms of MS may also impact on cognitive function, most notably fatigue, depression and chronic pain, although the current evidence for this is mixed.

1.4.6.1. Fatigue

Fatigue is often considered to be the most prevalent symptom of MS, and has been estimated to affect up to 90% of patients with MS (Bol et al., 2009), impacting significantly on level of disability and quality of life (Amato et al., 2001). Fatigue has been shown to impact on cognition both in healthy control (DeLuca, 2005) and MS participants, although the extent to which it contributes to cognitive impairment in MS is still debated. In MS populations fatigue has been associated with reduced performance on tasks of memory, executive function (e.g. planning) (Krupp & Elkins, 2000) and information-processing speed (Diamond, Johnson, Kaufman, & Graves, 2008). However, several studies suggest there is no evidence-based relationship between self-reported fatigue and cognitive performance in MS (e.g. Bailey et al., 2007; Parmenter, Denney, & Lynch, 2003), and further research exploring the association between objective fatigue measures and cognitive performance would be informative.

1.4.6.2. Mood

The lifetime prevalence rate of depression among the MS population, estimated at about 50% (Arnett & Strober, 2011; Goldman Consensus Group, 2005; Marrie, Cutter, Tyry, Campagnolo, & Vollmer, 2009), is higher than for the general population and this is generally thought to be an underestimation. Using the Beck Depression Inventory (BDI), many studies have found that a significantly greater number of patients with MS reach the cut-off criteria for depression relative to healthy controls (e.g. Mattioli, Bellomi, Stampatori, Parrinello, & Capra, 2011; Sundgren, Maurex, Wahlin, Piehl, & Brismar, 2013). Similar findings have resulted from studies involving other measures of mood such as the Centre for Epidemiologic Studies Depression Scale (CESD; Marrie et al., 2009) and the Hospital Anxiety and Depression Scale (HADS; Honarmand & Feinstein, 2009). This higher prevalence among the MS populations has been attributed to numerous factors including disease-related changes in the brain, fatigue, pain, level of physical disability and reduced quality of life (Arnett, Barwick, & Beeney, 2008).

In patients with MS who also suffer from depression, depression has been correlated with reduced information-processing speed, new learning and memory (Demaree, Gaudino, & DeLuca, 2003; Diamond et al., 2008) as well as executive function deficits (Arnett, Higginson, & Randolph, 2001) relative to non-depressed patients with MS. Thus, depression may impact patients' understanding and recall of complex treatment-related risk information. However, as with fatigue, other studies have not found significant correlations between cognitive function and depression in MS (e.g. Karadayi, Arisoy, Altunrende, Boztas, & Sercan, 2014; Mattioli et al., 2011).

1.4.6.3. Pain

Pain is another common symptom experienced by patients with MS although the extent to which it is viewed as a severe, disabling symptom depends on factors such as disease stage and severity as well as the location of the brain lesions (Foley et al., 2013). Pain has been shown to reduce performance on cognitive tasks in many individuals including on tests of attention, executive function, memory and general cognitive function (Moriarty, McGuire, & Finn, 2011).

1.4.7. Section Summary

There is evidence of cognitive impairment in MS, estimated to occur in 40-70% of cases. A specific profile of cognitive deficits in MS is emerging. Information-processing speed is the most common deficit along with impairments in new learning and memory. Executive function and attention are also affected, while language comprehension is typically spared. Recent evidence suggests that information-processing speed is the primary cognitive deficit in MS and may account for difficulties in other cognitive domains such as memory, new learning and executive function. In addition to findings of low numeracy in people with MS and the general population, as well as reduced risk awareness in MS, MS-related cognitive impairments may further impact on patients' ability to understand and recall treatment-related risk information. Furthermore, common MS symptoms of fatigue, depression and pain may also adversely affect cognitive function in MS, although research does not yet provide substantive support for this. Together, these findings again suggest that future research into modes of information presentation which reduce the impact of information-processing speed deficits and poor initial learning

may be beneficial in facilitating greater risk awareness in MS. However, researchers would firstly benefit from a greater understanding of the cognitive correlates of risk awareness in MS.

1.5. Impact of MS-Related Cognitive Impairment on Risk Awareness

In the context of the current study, risk awareness is operationalised as the capacity for new learning, understanding, and later recall of presented treatment information. This is similar to the construct of ‘capacity’ as used in everyday clinical practice (Grisso & Appelbaum, 1995). Capacity to make informed decisions about one’s care purportedly requires four main cognitive abilities: (i) *understanding* of relevant information, (ii) *reasoning* with treatment-related risks and benefits, (iii) *appreciation* of the significance of this information and (iv) *expression* of choice (Grisso, Appelbaum, & Hill-Fotouhi, 1997). Neuropsychological deficits may compromise some or all of these abilities (Basso et al., 2010). Risk awareness is typically evaluated by examining one’s ability to make informed decisions.

While MS-relevant studies are scarce, much research has documented correlations between specific cognitive functions (e.g. working memory, new learning, executive function, attention) and treatment-related decision-making in other cognitively-impaired populations, particularly dementia and Parkinson’s disease. Overall, problems in understanding appear most common across disorders (Basso et al., 2010) and are impacted primarily by memory and executive function deficits. Like other neurological disorders such as dementia and Parkinson’s, MS also involves memory and executive function difficulties. Thus, it is not unreasonable to expect that patients with MS would also struggle to understand, reason with and

appreciate risk information. It is also logical to surmise that reduced information-processing speed, the most common MS-related cognitive deficit, may limit the amount of information initially registered, again limiting understanding.

Only recently have studies begun to directly examine this relationship between cognitive deficits and informed decision-making in MS. Patients with MS who also had neuropsychological deficits performed significantly worse than a group of MS patients without neuropsychological deficits and a healthy control group on an Understanding Treatment Disclosures Scale (UTD). Moreover, poor understanding of treatment information correlated with reduced capacity for new learning as well as executive dysfunction (Basso et al., 2010).

McKnight (2007) developed the Test of Reasoning using Statistical Information (TRUSI) - a measure of statistical reasoning which includes an assessment of reasoning ability in relation to MS-related risk. Participants with MS demonstrated significantly weaker performance on this test relative to control participants. This finding was not replicated by Hans (2009). However, both studies revealed substantial correlations between statistical reasoning and cognitive functions of WM, sustained attention, processing speed and other reasoning domains. This suggests that patients with MS who have cognitive impairment in these domains may also have difficulties in reasoning about proposed treatments.

A more recent study employed the Game of Dice Task (GDT) to explore correlations between working memory, executive function and decision-making in MS. This is a decision-making task in which participants are presented with probabilistic risk information on potential gains and losses. Working memory deficits

and reduced information-processing speed correlated with more risky decisions but there was no correlation between executive function and decision-making in the context of risk-based decisions. Where information-processing speed and working memory deficits were more pronounced, those patients tended to make decisions involving higher levels of risk (Farez, Crivelli, Leiguarda, & Correale, 2014). These findings suggest that impairments in working memory or information-processing speed may impact on decision-making in the context of risk information. Notably, this study lacked a treatment-related risk context. Perceived importance of the risk-based decision may impact on an individual's effort or performance in terms of understanding, appreciating, reasoning and making decisions when presented with risk information.

Of course, other MS-related cognitive functions, such as complex attention or information-processing speed, and their relation to treatment-related decision-making capacity have not yet been explored fully. Once investigated, researchers will know more about how best to present treatment-related risk information in MS settings and which cognitive deficits to target. This is important given the emphasis on shared-decision making in clinical settings. Nonetheless, some studies have already begun to explore how different methods of presenting information to people with MS might improve risk understanding and recall by attempting to target these cognitive deficits.

1.5.1. Section Summary

Cognitive deficits may impact on an individual's risk awareness including their capacity to (i) understand, (ii) reason with, and (iii) appreciate treatment-related risk information and to (iv) express a choice regarding their medical care. Across a range

of disorders, reduced understanding of risk appears to be most commonly compromised. Cognitive deficits in working memory and executive function appear to correlate most often with this reduced understanding of risk.

Studies have only recently begun to explore the cognitive correlates of reduced risk awareness in MS. The findings to date suggest that people with MS may also demonstrate reduced understanding of risk which also appears to correlate with MS-related working memory and executive function deficits. Deficits in working memory, executive function, information-processing speed or attention in MS may also correlate with reduced ability to reason with risk information. Future research and replication studies are necessary to fully elucidate the cognitive correlates of reduced risk awareness in MS which in turn could inform clinical practice. In particular it could help to highlight alternative modes of presentation of information in clinical settings.

1.6. Presentation of Treatment-Related Information in MS

1.6.1. Repetition

A series of studies by DeLuca and colleagues found that additional learning trials enabled participants with MS to perform as well as controls on verbal recall and recognition tasks (DeLuca et al., 1998; 1994). This suggests that repetition of treatment information may increase learning, understanding and recall of risk information in MS. However, this group also argues that simple repetition alone is not always sufficient and that individuals with MS may require more intensive strategies to improve new learning and memory (Chiaravalloti, Demaree, Gaudino, & DeLuca, 2003).

1.6.2. Self-generation

Self-generated learning refers to a strategy whereby individuals generate their own ideas, images, or words to aid recall of presented information (Slamecka & Graf, 1978). Self-generated information requires more attention and effort than didactic information, is more deeply encoded and thus better remembered (Goverover, Basso, Wood, Chiaravalloti, & DeLuca, 2011). One study demonstrated significant improvements in recall of sentence endings in MS following a sentence-completion task relative to a didactic task (i.e. whole sentence heard) (Goverover & DeLuca, 2002). While, these participants with MS did not have memory impairments, it was later found that MS patients with memory impairment also benefit from self-generation (Basso, Ghormley, Lowery, Combs, & Bornstein, 2008). However, a more recent study has noted that the benefit of self-generation for learning and memory in patients with MS is dependent on intact executive functions (Goverover, Chiaravalloti, & DeLuca, 2013). Despite poor ecological validity, these studies suggest that participants with MS may also show benefits of self-generation in understanding and recall of treatment-related risk information in clinical settings.

1.6.3. Pacing

‘Pacing’ refers to the presentation of information at a slower rate than is normal. A recent study revealed a benefit of pacing in MS. MS and healthy control participants were presented with two aural extracts detailing fictitious health information, one at a slow rate and the other at a fast rate. As expected, the MS group recalled significantly less information than the control group. Interestingly, slowed presentation led to

significantly improved recall of health information in both groups. Information-processing speed partly accounted for this effect (Lloyd, 2012).

Another study explored whether slowed presentation of the Rivermead Behavioural Memory Test led to improved recall memory in MS. They found that participants with MS could recall significantly more elements of the presented stories in the slow presentation condition relative to the fast presentation condition for both immediate and delayed recall, with this effect being more pronounced for delayed recall. Furthermore, this was the case for participants with MS with and without verbal memory problems (Arnett, 2004). Based on these findings, Arnett (2004) also hypothesised that processing-speed may explain the benefits of slowed presentation immediate and delayed recall memory in MS.

1.6.4. Spacing

Another possible method of communicating treatment information in MS is based on the spacing effect, a phenomenon whereby learning trials presented over time and interspersed with breaks lead to greater retention rates than with massed presentation (i.e. consecutive trials) (Ebbinghaus, 1964). This effect has been well-established in the general population for example in advertising and consumer memory (Janiszewski, Noel, & Sawyer, 2003) and student learning (Carpenter, Cepeda, Rohrer, Kang, & Pashler, 2012). It has also been demonstrated in clinical populations, for example, traumatic brain injury (TBI) and amnesia.

Patients with amnesia were presented with word-lists that were either repeated altogether (massed) or with spaces in-between (spaced). Patients demonstrated enhanced recall and recognition of this word-list in the spaced relative to the massed

condition (Cermak, Verfaellie, Lanzoni, Mather, & Chase, 1996). It was hypothesised that this benefit of presenting trials over time, rather than in succession, is partly due to the greater information-processing time afforded by the delay between trials.

Using a TBI sample, participants heard a large word list either once (massed condition), twice consecutively (massed with repetition condition) or twice in smaller word blocks (spaced condition). Participants recalled significantly more words in the spaced condition relative to the massed conditions indicating that spaced presentation may improve learning in individuals with TBI (Hillary et al., 2003). A later, more ecologically valid TBI study revealed a significantly greater benefit of spaced presentation for learning of functional tasks, relative to massed presentation. Thus, distributing the presentation of trials over time facilitated more learning (Goverover, Arango-Lasprilla, Hillary, Chiaravalotti, & DeLuca, 2009a).

Only two studies, to this author's knowledge, have explored the potential benefits of the spacing effect in MS, although neither do so in the context of risk information. The first engaged MS and healthy control participants in verbal (paragraph learning) and visual (route learning) learning tasks. In the spaced condition, the task was presented three times with a 5-minute break during the intervals. In the massed condition, the task was presented consecutively three times. All participants performed significantly better on verbal recall and recognition tasks in the spaced condition relative to the massed condition, with no difference in the level of 'spacing' benefit between the groups (Goverover, Hillary, Chiaravalloti, Arango-Lasprilla, & DeLuca, 2009b). This suggests that presenting information in chunks over time facilitates better verbal learning and memory in MS. The authors note that the spacing effect is typically greater for more meaningful information and

for information that is semantically complex rather than structurally complex, something which has also been mooted by others (e.g. Janiszewski et al., 2003).

This group later hypothesised that self-generation and spaced learning together would lead to significantly enhanced learning and memory when compared with spaced learning alone. Participants performed three functional tasks (learning names, appointment times and object locations) in three conditions (massed, spaced, spaced with self-generation). Recall was best in both MS and healthy control participants for the ‘self-generation with spaced learning’ condition across all three tasks, thus supporting their hypothesis. However, recall in the ‘spaced learning’ condition was also significantly better relative to the ‘massed’ condition, again demonstrating the usefulness of this strategy in improving learning and memory in MS (Goverover et al., 2011).

One limitation of these studies is the difficulty in separating the effects of repetition and spacing, especially as repetition alone can improve learning (DeLuca et al., 1998; DeLuca, Leavitt, Chiaravalloti, & Wylie, 2013). Moreover these spacing studies focus on new learning and memory for simple everyday tasks rather than for complex risk information. Yet it has been shown that learning and memory deficits impact on MS-related risk awareness (e.g. Basso et al, 2010). Thus, it was felt that it would be worthwhile exploring the efficacy of spacing in facilitating greater risk awareness in MS in clinical settings as well as exploring the benefit of spaced presentation separate from the benefit of repetition.

1.6.5. Section Summary

Limited research has been carried out to determine the ways in which presentation of information can be adjusted to facilitate improved learning and memory of new information in MS. While repetition of information demonstrates limited benefits, self-generation, pacing and spacing of information show promise in aiding learning and recall in MS. Pacing and spacing are thought to facilitate improved learning and recall by allowing extra time to process information, thus reducing the effects of information-processing speed deficits common in MS. However, these studies lack ecological validity. None explore the benefits of such strategies in a clinical setting, to aid understanding and recall of risk-information regarding potential treatment options.

1.7. Rationale behind Efficacy of Spaced Presentation in Improving Learning and Memory in MS

Given the ample evidence which points towards reduced information-processing speed as the primary deficit in MS, one may suppose that the spacing effect affords greater time to process new information. Certainly, this is the view which has been advocated by the few studies which have explored the benefits of the spacing effect for learning and memory in MS (Goverover et al., 2009b; Goverover et al., 2011) as well as in other neurological conditions (e.g. Cermak et al., 1996; Goverover et al., 2009a).

Theories of memory and encoding also provide an insight into the possible workings of this spacing effect. One theory moots that a natural ‘encoding deficit’ becomes evident during massed presentation because the initial stimulus remains in WM while the second stimulus is presented. Conversely, spaced items benefit from

more time alone in WM and receive greater attention than do consecutively presented items, thus strengthening the memory trace (Braun & Rubin, 1998). The ‘deficient processing hypothesis’ postulates that consecutive repetition causes habituation to that stimulus, leading to less processing and therefore reduced benefit of repetition (Hintzman, 1974). Since MS-related memory difficulties likely occur at encoding, these natural encoding phenomena may be more pronounced in MS, leading to a more prominent difficulty. This provides further rationale for additional exploration of the benefits of spaced presentation in MS.

1.8 Outline of Research

1.8.1. Objectives of the Proposed Study

The present study aimed to establish whether the spacing effect could be used to facilitate greater risk awareness in people with MS within a health context. Specifically, it investigated whether spaced presentation of risk information could improve understanding and recall of treatment-related risk information in people with MS. It extended literature from cognitive rehabilitation in MS by exploring the potential benefit of spaced presentation using aural information detailing realistic risk-benefit treatment information. In doing so, this study provided a more ecologically valid examination of the spacing effect in MS than has been carried out to date which may hold practical value in clinical settings. This study also examined the cognitive correlates of understanding and recall of treatment-related risk information. Finally, this study attempted to distinguish the effects of repetition and spacing by presenting information which was broken into chunks and heard just once, rather than repeating the same trial interspersed with breaks as in previous studies.

1.8.2. Rationale for the Proposed Study

With the development of newer, more efficacious second-line MS medications which carry potentially life-threatening side effects, patients with MS must comprehend complex risk-benefit information regarding potential MS treatments. Furthermore, the promotion of a shared decision-making (SDM) model within health settings means patients must also use this complex information to make decisions regarding their medical treatment. Yet, numerous studies have documented reduced risk awareness in MS which may be associated with the well-documented cognitive impairments of reduced information-processing speed, memory and new learning in MS.

While the provision of EBPI can improve risk knowledge in MS, inadequate risk awareness persists in a high proportion of patients. This suggests that that an increase in the quantity of information (i.e. EBPI alone) is unlikely to facilitate greater risk awareness in the majority of this population. Limited research has explored ways of facilitating greater learning and recall in MS by altering the mode of information presentation. However no study has explored the benefit of such methods in facilitating greater risk awareness in MS. Several recent studies have provided tentative evidence for the benefits of different presentation formats in facilitating greater recall of information in MS. Repetition, pacing, self-generation and spacing of information have all been shown to improve recall in MS, seemingly because this reduces the impact of information processing speed deficits.

The current study draws on prior research by Goverover and colleagues (2009a; 2009b; 2011) who report a benefit of the spacing effect in facilitating greater verbal recall memory in MS and TBI. Hillary and colleagues (2003) also reported a

benefit of the spacing effect in facilitating verbal memory recall in patients with TBI who, like patients with MS, have been shown to suffer from encoding memory deficits. The current study builds on such research by exploring the benefits of spaced presentation in facilitating greater risk awareness in MS, specifically greater understanding and recall of treatment-related risk information. The use of aurally-presented fictitious information which describes realistic risk-benefit ratios of various treatment options offers a more ecologically valid study of the spacing effect. This will help to establish the potential clinical effectiveness of spaced presentation and its ability to aid the advancement of true SDM.

Finally, the current study is the first, to this author's knowledge, which has attempted to distinguish the effects of repetition and spacing by presenting information which was presented just once in either a massed or spaced format. It is also the first to include a massed-with-delay condition in order to ascertain whether an otherwise significant benefit of spaced presentation could be confounded by time delay during the 'spaces' and the effect of this delay on recall.

1.8.3. Research Questions

1. Does spaced presentation of treatment-related risk information lead to improved understanding and recall of risk information in all participants when compared to massed presentation?
2. Are people with MS differentially affected by spaced presentation of treatment-related information relative to healthy controls in terms of recall and understanding of risk information?

3. What are the specific cognitive functions associated with understanding and recall of treatment-related risk information?

1.8.4. Hypotheses

1. It was hypothesised that the MS group would understand and recall significantly less treatment-related risk information relative to the healthy control group in all presentation conditions.
2. It was hypothesised that the spaced presentation of treatment-related risk information would significantly improve recall and understanding of treatment-related risk information in both MS and healthy control participants relative to massed presentation of information.
3. It was hypothesised that there would be a greater benefit of spaced presentation of risk information in the MS group relative to the control group.
4. The specific cognitive correlates of understanding and recall of treatment-related risk information were explored. It was hypothesised that reduced speed of information-processing would be associated with reduced recall and understanding of treatment-related risk information in both the MS and healthy control group.

2. Method

2.1. Research Approval

The project received ethical approval from the NHS National Research Ethics Service following Proportionate Review (see Appendix A). The Research and Development department of University College London Hospitals NHS Foundation Trust gave permission for the recruitment of the MS group from the National Hospital for Neurology and Neurosurgery (NHNN) (see Appendix B). Finally, ethical approval was also obtained from the Research Ethics Committee, Royal Holloway, University of London.

2.2. Design

The project employed a cross-sectional mixed experimental design to test the effects of presentation format on participants' recall and understanding of risk information. A neuropsychological test battery was also administered. A 3 X 2 mixed model was used to explore differences in recall and understanding of risk information across different modes of information presentation (within-subject variable) between MS and healthy control participants (between-subject variable). The within-subject variable (presentation format) had three levels (massed, massed-with-delay, spaced). The between-subject variable (group) had two levels (MS; healthy control). The primary dependent variables were immediate recall score and understanding of risk information score. Groups were matched on age, gender and pre-morbid intellectual functioning.

2.3. Participants

A total of 60 participants were recruited for the study; 30 MS participants and 30 healthy control participants. Suitability for participation was assessed using the following inclusion and exclusion criteria.

Inclusion criteria:

- English as a first language
- Aged between 25-60 years
- For MS participants only: A definite clinical diagnosis of MS (relapsing-remitting, primary progressive or secondary progressive) by a Consultant Neurologist in accordance with the McDonald criteria (McDonald et al., 2001)

Exclusion criteria:

- History of a neurological or other medical condition, other than MS for the MS group, that may impact cognition
- A previous or current significant psychiatric diagnosis
- Current or previous history of drug or alcohol misuse
- A significant visual or hearing impairment that would interfere with the person's ability to engage with cognitive testing
- Lack of mental capacity to provide informed consent
- For MS participants only: Currently experiencing a relapse of MS, defined as a recent exacerbation of symptoms or presence of new symptoms up to 28 days prior to the study

- For MS participants only: significant change to medication regime up to 28 days prior to the study

2.4. Recruitment

2.4.1. MS Participants

The MS group was recruited from a database held at the London-based National Hospital for Neurology and Neurosurgery (NHNN). This database contained a list of patients with MS who had previously expressed an interest in being contacted regarding upcoming research studies. Potential participants were identified by a member of the patients' direct healthcare team (Clinical Psychologist, Clinical Nurse Specialist and Consultant MS Nurse). An invitation letter (see Appendix C), participant information sheet (see Appendix D) and reply form were then sent to these patients via post. Participants contacted the MS researcher directly to express interest in the study by returning the reply form. The MS researcher then contacted each participant by telephone to discuss the study in more detail and answer any questions. All participants were assured that their participation was entirely voluntary and that a decision to decline to take part would not have any impact on their ongoing provision of medical care. All MS participants completed the study in their own homes.

2.4.2. Healthy Control Participants

In order to ensure that the MS and healthy control groups were matched on gender, age and pre-morbid intellectual function, recruitment of healthy control participants began only once an indication of age, pre-morbid intelligence level and gender began to emerge in the MS sample.

Healthy control participants were recruited through several avenues: An opportunistic sampling approach was employed in recruiting within friends and family networks (London-based) who were sent an invitation letter and information sheet via email or post (see Appendix E and Appendix F). Additionally, letters of request were sent to a named representative within personnel departments of local companies (i.e. London-based) (see Appendix G), along with an information sheet. All participants were given information sheets (see Appendix F) and those interested in the study contacted the researcher directly. A subsequent telephone conversation was arranged to further discuss the study and answer any questions. Healthy control participants were given the choice to complete the study at their home (friends or family only), place of work, or at a central London office belonging to Royal Holloway, University of London.

2.4.3. All participants

All participants were given at least two weeks prior to commencing the study to decide whether or not to partake. After this time, the researcher contacted them to arrange a study visit. Written informed consent was obtained from each participant before commencing any study tasks (see Appendix H for MS consent form and Appendix I for Healthy Control consent form).

2.5. Safety Protocol

A protocol which followed the Guidance from the National Health Service Lone Worker Policy (NHS Security Management, 2005) was established in order to ensure the researcher's safety when undertaking study sessions, particularly in participants' homes. All MS participants were known to their clinical care team and had undergone

previous home visits as part of their care. All healthy control participants were seen either at a central London location belonging to Royal Holloway, University of London, or at their place of work. Only those healthy control participants personally known to the researcher were seen at home.

2.6. Power Analysis

The sample size was calculated from a power analysis based on the expected findings from the primary outcome (i.e. whether a spaced presentation format improves recall and understanding of risk information). A 3 X 2 mixed analysis of variance (ANOVA) was the intended analysis for the main dependent variable (immediate recall) with 'presentation format' (spaced, massed, or massed-with-delay) as the within-subject variable and 'group' (MS or healthy control) as the between-subject factor.

Using participants with traumatic brain injury, Hillary and colleagues (2003) compared the benefits of spaced versus standard presentation on a word-list learning and recall task. They found a significant benefit of spaced presentation with an effect size of partial $\eta^2 = .37$. This is considered a medium effect size according to Cohen's classifications (Cohen, 1992).

G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) was used to compute the power analysis. Considering the planned analysis (ANOVA), the anticipated medium effect size, the alpha level set at 0.5 and power set at 0.7, a sample of 60 participants was recommended. Therefore, a minimum of 30 MS and 30 healthy control participants was deemed sufficient for the current study.

2.7. Assessment Procedure

Participants were informed that study visits would last approximately two hours. Each visit began with the researcher providing an explanation of the study and participants were invited to ask questions. Written informed consent was received before the commencement of any study tasks and participants were reminded that they may withdraw at any time.

All participants were offered the opportunity to receive feedback on the results of the study. Those interested in feedback granted permission for their contact details to be temporarily retained and they were provided with an estimated date of feedback.

Relevant demographic and clinical information was obtained for each participant; including age, date of birth, level of education, occupation, history of any neurological condition or significant psychiatric illness, and sensory impairments including hearing and vision. This information was obtained from the medical notes and patient self-report. MS participants also detailed their MS diagnosis (RRMS, PPMS, or SPMS), date of last relapse, whether they had fully recovered since their last relapse and any significant recent medication changes (< 28 days).

2.8. Materials and Order of Test Administration

The order of measures and test administration is outlined in Table 1. Participants first completed baseline measures of mood (Hospital Anxiety and Depression Scale, HADS; Zigmond & Snaith, 1983) and fatigue (Fatigue Severity Scale, FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) and a baseline measure of comprehension (MTT). These indicated the level of anxiety, depression and fatigue symptoms

experienced by participants in everyday life. Participants then completed the experimental measure which was interspersed with several neuropsychological tests. On completion of the experimental measure, further neuropsychological tests were administered as well as a measure of statistical reasoning (TRUSI-B).

Table 1

Order of Measures and Test Administration

Study procedure	Test order
Baseline measures & measure of comprehension	<ol style="list-style-type: none"> 1. FSS 2. HADS 3. Modified Token Test (MTT)
Experimental tasks (with some neuropsychological testing)	<p>Order of presentation format was counterbalanced across participants. One example of the order of presentation format is:</p> <ol style="list-style-type: none"> 1. Standard presentation of Vignette A 2. Spaced presentation of Vignette B 3. Standard presentation-with-delay of Vignette C <p>Wechsler Test of Adult Reading (WTAR), Symbol Digit Modalities Test (SDMT), & Arithmetic subtest (WAIS-III) administered during delays.</p> <p>See Table 2 for detailed description of each experimental condition</p>
Neuropsychological testing (continued)	<ol style="list-style-type: none"> 1. California Verbal Learning Task (CVLT-II) first five recall trials 2. The Verbal and Spatial Reasoning Test - Verbal Analogies subtest 3. The Verbal and Spatial Reasoning Test - Verbal Series subtests 4. Test of Reasoning Using Statistical Information Version B (TRUSI-B)

2.8.1. Experimental Measure:

The experimental measure consisted of three short aural extracts, or vignettes, which were heard by all participants. These vignettes were played to participants in audio tape format to allow for consistency across all participants. Each vignette provided information about one of three different fictitious diseases (Durkins Disease, Shannon's Disease, Raylick's Disease) and two fictitious drug treatments for each (Ganlin and Tylon, Limac and Braddex, Trixon and Fylene) (see Appendix J). Each was designed to replicate the type of information provided to patients during clinical consultations. As such, these vignettes detailed the symptoms, prognosis, treatments, and treatment side-effects and benefits for each fictitious disease. Information leaflets written by the pharmaceutical companies detailing side-effects of some common MS and non-MS medications were referred to when choosing the wording of symptoms and the format of numerical and statistical risks for the current vignettes. Again, this was to ensure that the style of information provided was similar to that which lay people are likely to encounter when making medical decisions. These vignettes were then reviewed by a neuropsychologist with much past experience in MS clinic settings and feedback was also sought from 5 MS participants during the pilot study. While these participants felt that the information contained in each vignette was rather complex, they all reported it to be of similar complexity to the type of treatment-related information they heard on receiving an MS diagnosis, albeit somewhat briefer.

Each vignette was presented in a different format which is detailed in Table 2 below. One vignette was presented in its entirety (massed presentation). Another was presented in three shorter segments of equal length with a 5-minute break between each segment (spaced presentation). The final vignette was presented in its entirety

followed by a 10-minute delay before recall (massed presentation with delay). This final presentation format was included because the primary outcome measure of the study is immediate recall. However, the time between participants receiving one-third of the information in the spaced condition and their recall of this information is approximately ten minutes. Therefore, the inclusion of a ‘massed with 10-minute delay’ condition helps to ascertain whether an otherwise significant benefit of spaced presentation could be confounded by time delay for recall of the blocked presentation.

Table 2

Composition of Experimental Conditions (Massed, Spaced and Massed-with-delay Presentation Formats)

Experimental condition	Order of tests
Massed presentation	<ol style="list-style-type: none"> 1. Vignette A presented in full 2. Immediate recall of vignette A 3. Measure of understanding of information for vignette A
Spaced presentation	<ol style="list-style-type: none"> 1. Vignette B (Part 1) presented 2. Wechsler Test of Adult Reading (WTAR) (during 5 minute interval) 3. Vignette B (Part 2) presented 4. Symbol Digit Modalities Test (SDMT) (during 5 minute interval) 5. Vignette B (Part 3) presented 6. Immediate recall of vignette B 7. Measure of understanding of information for vignette B
Massed presentation with delay	<ol style="list-style-type: none"> 1. Vignette C presented in full 2. Arithmetic subtest from Wechsler Adult Intelligence Scale Third Edition (WAIS-III) (during 10-minute interval) 3. Recall of vignette C 4. Measure of understanding of information for vignette C

Immediate recall and understanding of risk information were assessed following each vignette. The vignettes and their corresponding scoring criteria were

developed specifically for the current study. As such there is no established validity or reliability for these measures. However, the development of each vignette and the scoring method applied for immediate recall was based on the style and scoring method used by several well-established neuropsychological tests of verbal memory, for example the BIRT Memory Information Processing Battery (BMIPB; Coughlan, Oddy, & Crawford, 2007). Participants received two points for correctly recalled elements of information and one point for each partially correct element. There were 35 elements of information within each vignette, with a maximum possible score of 70 points (see Appendix K for sample record form and Appendix L for scoring examples). This score was then translated into a ‘percentage correct’ score indicating the amount of the vignette accurately recalled by each participant.

Understanding of the risk information was measured after each vignette using a set of eight questions designed to capture participants’ understanding of numerical and verbal risk information (see Appendix M). Again, participants received two points for correctly recalled items and one point for each partially correct item (see Appendix N for scoring examples). A maximum total score of 16 was possible and total scores were converted into a ‘percentage correct’ score prior to data analysis.

Each vignette was approximately two minutes in duration. A timeline highlighting the equivalence of timings for each presentation format and interim neuropsychological tests is provided in Table 3 below.

Table 3

Design Schedule Depicting the Timings for Each of the Three Presentation Formats – Massed, Massed-with-delay, and Spaced.

Minutes	Vignette A Massed presentation	Vignette B Spaced presentation	Vignette C Massed-with-delay presentation
1-2		X	X
3-4			X
5-6			
7-8		X	
9-10			
11-12	X		
13-14	X	X	
15-16	Recall	Recall	Recall

Note. X indicates start time of each presentation condition or neuropsychological test.

Elements of the neuropsychological test battery were administered in the 5-minute (i.e. during the ‘spaced’ presentation condition) and 10-minute (i.e. during the ‘massed-with-delay’ presentation condition) delay periods. An effort was made to ensure that these tasks were relatively low-level so as not to interfere with recall and understanding of the presented risk information. The tests administered during these breaks were kept constant for all participants so as not to add a further confounding variable.

To control for potential order effects, the order of presentation of format was counterbalanced across participants using a Latin Square. This ensured that similar numbers of participants heard the three fictitious vignettes (Durkins disease, Shannon’s disease and Raylick’s disease) in each sequence of the three presentation formats (massed, massed-with-delay, spaced). Using a Latin Square, three different combinations of order of vignette presentation format were possible (see Table 4 and Table 5).

Table 4

Latin Square Presentation Formats

A	B	C
B	C	A
C	A	B

Note. Where A = massed, B = spaced, C = massed with delay

Table 5

Latin Square Resulted in the Following Three Possible Sequences of Presentation

Format for Each of the Three Disease Vignettes

Sequence 1	A1	B2	C3
Sequence 2	B1	C2	A3
Sequence 3	C1	A2	B3

Note: Where A = massed, B = spaced, C = massed with delay; 1 = Durkin’s disease vignette, 2 = Shannon’s disease vignette, 3 = Raylick’s disease vignette

For example, Sequence 1 was selected as the initial block in the MS group.

This refers to the A1-B2-C3 sequence. Therefore the first MS participant heard the vignette for Durkin’s disease in the ‘massed’ condition, then Shannon’s disease in the ‘spaced’ condition, followed by Raylicks disease in the ‘massed-with-delay’ condition. An equal number of participants (n=10) in both the MS and healthy control groups completed each of the three different sequences.

2.8.2. Neuropsychological Test Battery and Measures

The neuropsychological test battery was administered for several reasons: (1) to explore whether any cognitive functions were correlated with understanding and recall of risk information; (2) to ensure that the MS sample was representative of the wider MS population in terms of cognitive ability, to enable generalisability of the results.

The neuropsychological test battery consisted of eight different measures assessing a range of cognitive functions. These measures are outlined in Table 6 below (also see Appendices O-X).

Table 6

Neuropsychological Test Battery and Corresponding Cognitive Domains Measured

Test	Cognitive domain measured
Wechsler Test of Adult Reading (WTAR; Holdnack, 2001)	Pre-morbid intellectual function
California Verbal Learning Task (CVLT-II) first five recall trials (Delis et al., 2000)	Immediate verbal recall & recognition memory
Arithmetic subtest from Wechsler Adult Intelligence Scale Third Edition (WAIS-III; Wechsler, 1997)	Working memory & arithmetic ability
The Modified Token Test (MTT; Coughlan & Warrington, 1978)	Comprehension
Symbol Digit Modalities Test, oral response form (SDMT; Smith, 1982)	Information processing speed
The Verbal and Spatial Reasoning Test - Verbal Analogies subtest (VESPAR; Langdon & Warrington, 1995)	Verbal inductive reasoning
The Verbal and Spatial Reasoning Test - Verbal Series subtests (VESPAR; Langdon & Warrington, 1995)	Arithmetic
Test of Reasoning Using Statistical Information Version B (TRUSI-B; McKnight, 2007; Hans, 2009)	Statistical reasoning

Given that motor impairments and chronic fatigue are common difficulties associated with MS, test selection considered those measures which do not rely heavily on motor skills and which are of relatively short duration in order to minimise the impact of such difficulties on test performance. Each measure is detailed below.

2.8.2.1. California Verbal Learning Test (CVLT-II):

The California Verbal Learning Test-2nd Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) consists of a 16-item word list which is read aloud to participants five times, at the rate of one word per second. Participants are asked to verbally recall as many words as possible following each trial. Both the CVLT-II and SDMT (outlined below) make up part of an MS cognitive screening battery known as the Brief International Cognitive Assessment for Multiple Sclerosis, which is recommended as a gold standard assessment of cognition in MS by an expert consensus group (BICAMS; Langdon, Amato, Boringa et al., 2012). The CVLT-II has been shown to have good test-retest reliability for healthy control (Delis et al., 2000; Woods, Delis, Scott, Kramer, & Holdnack, 2006) and MS participants (Benedict, 2005; Delis et al., 2000). It also has high construct, concurrent and external validity in people with MS and the total recall score obtained from the five consecutive trials used in this study has been shown to reliably distinguish MS participants from healthy controls (Stegen et al., 2010).

2.8.2.2. Symbol Digit Modalities Test (SDMT):

The Symbol Digit Modalities Test (SDMT oral form; Smith, 1982) is a measure of information-processing speed. Participants are presented with a visual key consisting of nine single digits, each matched to a particular abstract symbol. Rows of

these abstract symbols are then presented and participants must verbally state which number corresponds with each symbol. The total score is the number of correct responses provided within a 90-second time limit. Importantly, this measure reduces the potential confounding effect of motor function with the oral response format. The SDMT has high test-retest reliability, good predictive and construct validity (Benedict et al., 2006) and can reliably indicate cognitive impairment and distinguish MS and healthy control participants (Benedict et al., 2006; Orchard, Giovannoni, & Langdon, 2013).

2.8.2.3. The Verbal and Spatial Reasoning Test (VESPAR):

The Verbal and Spatial Reasoning Test (VESPAR; Langdon & Warrington, 1995) was designed to minimise the effects of sensory, motor or cognitive impairments on performance on tests of reasoning ability in adults with a neurological condition (Langdon & Warrington, 2000) and has been used to assess verbal and spatial reasoning in MS populations. It comprises six subtests, two of which are included in the present study and consist of 25-items: the Verbal Analogies subtest which measures verbal inductive reasoning by analogy and the Verbal Series subtest which measures numerical inductive reasoning by series completion. In Verbal Analogies, each item consists of a word pair containing two related words, followed by a single word and four potential matches. Participants choose the word which best fits with the single word to form a second word pair with the same relation as the initial word pair. In Verbal Series, participants are given three numbers which form a particular numerical pattern and are asked to choose which of four other numbers best completes this pattern.

2.8.2.4. Arithmetic Subtest of Wechsler Adult Intelligence Scale-Third Edition

(WAIS-III):

The Arithmetic subtest from the Working Memory Index of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997), a measure of general cognitive functioning for adults aged 16 to 89 years, was employed in the present study in order to evaluate working memory and arithmetic ability. This subtest consists of 20 timed mental arithmetic problems of graded difficulty. These are read aloud to participants who must solve them without the assistance of paper, pen, calculator or other aid. The WAIS-III has established validity and reliability. Studies have demonstrated high internal consistency ($\alpha=.94-.98$) and high inter-rater reliability ($\alpha\geq.90$) for most subtests. There is also evidence of high concurrent and construct validity across subtests (Wechsler, 1997). The WAIS-III is a valid measure of differentiating between individuals with and without a neurological condition, including MS (Smith, Cerhan, & Ivnik, 2003).

2.8.2.5. Test of Reasoning Using Statistical Information (TRUSI):

The Test of Reasoning Using Statistical Information (TRUSI; McKnight, 2007) requires participants to apply statistical reasoning across three different categories of questions; general everyday risks, health-related risks, and MS-specific health-related risks. Each of these three sections consists of eleven multiple choice questions. One point is allocated for each correct response, with a maximum total score of 33. The TRUSI is a reliable and valid measure of statistical reasoning ability in MS and again enables discrimination between MS and healthy control samples (Hans, 2009). It

possesses good concurrent validity with other measures of reasoning and arithmetic ability as well as good internal consistency for all three sections (between 0.74-0.8).

2.8.2.6. Wechsler Test of Adult Reading (WTAR):

The Wechsler Test of Adult Reading (WTAR; Holdnack, 2001) was included in the test battery as a measure of pre-morbid intellectual function. This was required to match MS and healthy control participants, ensuring that both groups did not differ significantly in their level of general intellectual functioning. The WTAR consists of 50 irregular words which are read aloud by participants. One point is allocated for each correct pronunciation (maximum 50 points). Total scores are converted into a WAIS-III Full-Scale IQ score. As reading is largely preserved following brain injury, even in the case of decline in other cognitive abilities (Lesak, Howieson, & Loring, 2004), WTAR scores provided a measure of MS participants' expected level of functioning prior to any MS-related cognitive decline. Concurrent validity correlation coefficients for the WTAR are high (range from $r=.75-.78$) when compared with the Reading subtest of the Wide Range Achievement Test-Fourth Edition (WRAT-IV) (Mullen & Fouty, 2014). The WTAR is strongly correlated with WAIS-III measures of verbal IQ, full-scale IQ and verbal comprehension (Spren & Strauss, 2006) and it has high test re-test reliability ($r=.90-.94$) (Holdnack, 2001).

2.8.2.7. Modified Token Test (MTT):

The Modified Token Test (MTT; Coughlan & Warrington, 1978) was adapted from DeRenzi's and Vignolo's (1962) longer Token Test. It was selected in this study to provide a brief measure of participants' ability to comprehend and follow verbal commands. Participants heard 15 requests to execute a particular action using

randomly placed shapes (e.g. “Put the red circle on the green triangle”). One point was awarded for each correct answer (maximum score=15). Participants who scored below the cut-off score (<12) are typically classified as having reduced verbal comprehension and these cut-off scores can effectively distinguish between healthy control participants and those with brain lesions resulting in comprehension impairment (Coughlan & Warrington, 1978).

2.8.2.8. Hospital Anxiety and Depression Scale (HADS):

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) is a self-report measure of anxiety and depression symptoms which is widely used in clinical settings and was designed to avoid overlap with those symptoms which may also be linked to physical or somatic illness, for example fatigue, insomnia, or appetite changes. In this way, it has greater power to detect depression and anxiety symptoms in those with a chronic physical illness such as MS (Zigmond & Snaith, 1983). It consists of 14 items (seven anxiety-related and seven depression-related items) which are scored on a 4-point scale from 0-3 (3 indicating greater symptom severity). Scores on both the anxiety and depression scale range from 0-21.

The HADS is also a valid measure of symptom severity and has good reliability in detecting depression and anxiety in the general population, mental health or primary care settings (Bjelland, Dahl, Haug, & Neckelmann, 2002; Zigmond & Snaith, 1983) as well as in MS (Watson, Ford, Worthington, & Lincoln, 2014). A large-scale review established the HADS to have good internal consistency for both anxiety (mean $\alpha=.83$) and depression (mean $\alpha=.82$) as well as good concurrent validity, correlating well with other measures of anxiety and depression ($r=.49-.83$)

including the Beck Depression Inventory (BDI) and General Health Questionnaire (GHQ) (Bjelland et al., 2002). This review also supported Zigmond's & Snaith's (1983) recommended cut-off scores for clinically significant depression and anxiety symptoms (normal (0-7), mild (8-10), moderate (11-14) and severe (15-21)).

2.8.2.9. Fatigue Severity Scale (FSS):

The Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) is a nine-item self-report measure of fatigue exploring the effects of fatigue on a range of functional activities (e.g. physical function, work and social life). Participants rate each item on a Likert scale from 1-7 (where 1 = strongly disagree, 7 = strongly agree), with a possible total score between 7-63. This total score can be averaged to get a mean score between 1-7 for each participant. It was originally developed to assist researchers in measuring fatigue within MS but has well-established validity and reliability in detecting the impact of fatigue on functional ability in other neurological and medical disorders (e.g. Grace, Mendelsohn, & Friedman, 2006; Rosa et al., 2014). It reliably distinguishes MS-related fatigue from fatigue experienced by healthy controls (Motl, McAuley, Wynn, & Vollmer, 2011). The FSS demonstrates high internal consistency ($\alpha=0.81$ for MS population, $\alpha=0.88$ for healthy population; Krupp et al., 1989), concurrent validity (e.g. correlates well with the VAS fatigue scale; Motl et al., 2011), and test-retest reliability (Krupp et al., 1989; Dittner, Wessley, & Brown, 2004).

2.9. The Pilot Study

A pilot study comprising five MS and five healthy control participants was conducted in order to enable development of the novel experimental procedure (i.e. aural extracts and measure of understanding of risk information) and the order of testing. No subsequent modifications were made to the experimental stimuli or testing order. Therefore, the data collected during the pilot study was included in the main analysis.

2.10. Main Analysis

Quantitative analysis was carried out using an advanced statistical software package, the IBM Statistical Package for the Social Sciences (IBM SPSS) version 21.0 for Windows (IBM Corp., 2012). Normality of distribution was assessed for all variables. Two variables were non-normally distributed. One of these variables (depression) was transformed so that it satisfied the conditions for parametric tests. The second variable (Modified Token Test raw scores) did not meet the assumption of normally distributed data even after trialling several different transformations. Therefore non-parametric tests were used in analysing this data (see section 3.1. for further details). The following parametric tests were used in examining group comparisons, cognitive variables and the experimental condition.

2.10.1. Group Comparisons

Independent sample t-tests were used to explore whether the groups were matched on age and pre-morbid intelligence. A chi-square test determined whether the groups were matched for gender. If the groups had differed significantly on one of these demographic variables, this variable would have been used as a covariate in

subsequent analyses in order to control for any possible influence on the outcome. However, this was not necessary in the present study. Independent sample t-tests were also used to determine whether the groups differed significantly in terms of self-reported depression, anxiety and fatigue.

2.10.2. Cognitive Variables

Independent sample t-tests were carried out to assess whether the two groups differed on any of the cognitive measures (i.e. Arithmetic subtest of WAIS-III, SDMT; CVLT-II, Verbal Analogies (VESPAR), Verbal Series (VESPAR), TRUSI-B). Bonferroni corrections were applied to account for the number of comparisons made. Significant group differences for any cognitive variables would undergo further exploratory analysis. Specifically, Pearson correlations would be performed to explore the associations between each of these cognitive variables and the dependent variables (i.e. recall and understanding of risk information). The non-parametric equivalent of an independent sample t-test, the Mann-Whitney U test, was used to explore group differences on the Modified Token Test (MTT).

2.10.3. Experimental Condition

The primary dependent variable was immediate recall scores as this was felt to reflect the amount of information which had been encoded by participants for each of the three presentation formats. This in turn has potential implications for an individual's ability to make informed healthcare decisions. A 3 X 2 mixed ANOVA was performed on the primary dependent variable (immediate recall) with presentation format ('massed' versus 'spaced' versus 'massed-with-delay') as the within-subject factor and Group (MS versus healthy control) as the between-subject factor. This

established whether immediate recall of health information differed between the MS and healthy control group and across different presentation formats. Significant results for presentation format were explored further using paired-sample t-tests.

The secondary dependent variable was the understanding of risk information scores. Another 3 X 2 mixed ANOVA was performed with presentation format ('massed' versus 'spaced' versus 'massed-with-delay') as the within-subject factor and Group (MS versus healthy control) as the between-subject factor to assess whether MS and healthy control participants differed in their level of understanding of health-related risk information and to investigate whether participants differed in their level of understanding of risk information across different presentation conditions.

3. Results

3.1 Exploratory Data Analysis

Quantitative analysis of the data was carried out using IBM SPSS version 21.0 for Windows (IBM Corp., 2012). Prior to analysis, the data was checked for missing values and overall accuracy of data entry. One MS participant failed to complete the TRUSI measure in its entirety resulting in eight missing values and was therefore excluded from analysis of this variable. There were no other instances of missing data for either group.

Distribution of the data was also assessed to establish whether the data met the assumption of normally distributed data for parametric analysis. As suggested by Tabachnick and Fidell (2007), a z-score cut-off of between -2.58 and 2.58 for both Skewness and Kurtosis was used to determine normality of distribution for each variable.

The Modified Token Test raw score was significantly negatively skewed in both the MS ($z=-6.46$) and healthy control ($z=-6.58$) groups. The depression raw score obtained using the HADS was significantly positively skewed ($z=4.18$) in the healthy control group only. Based on Tabachnick and Fidell's (2007) recommendations for moderately positively skewed data, the depression raw scores were transformed using square root transformations via the $\text{SQRT}(X)$ function (i.e. taking square root of all raw scores to bring larger scores closer to the centre; Field, 2005). This transformation produced normally distributed data for the Depression raw score across both groups (see Appendix W).

Using Tabachnick and Fidell's (2007) recommendations for severely negatively skewed data, inverse (reciprocal) transformations were used to transform the substantially negatively skewed data for the Modified Token Test using the $1/(K-X)$ function. However, the Modified Token Test raw score remained significantly negatively skewed across both groups. Therefore, the non-parametric equivalent of an independent sample t-test, the Mann-Whitney U test, was used to explore group differences on the Modified Token Test (MTT).

3.2. Demographic and Clinical Variables

Descriptive statistics were calculated for each of the demographic and clinical variables of interest for both the MS and healthy control groups. These included gender, age and pre-morbid intelligence function (see Table 7) and fatigue, anxiety and depression.

3.2.1. Gender

The ratio of male to female participants was 10:20 in the MS group and 14:16 in the healthy control group. A Chi-square analysis revealed no significant difference between the groups in terms of gender ($\chi^2 (1) = 1.11, p = .29$). Therefore, the two groups were matched on gender and this variable was not considered in any subsequent analysis.

Table 7

Summary of the Descriptive Statistics for the Demographic Variables of Gender, Age and Pre-morbid Full-Scale IQ Scores across the MS and Healthy Control Groups

Group	Gender	Age		Pre-morbid FSIQ	
	Male:Female	M (SD)	Range	M (SD)	Range
MS	10:20	49.7 (8.3)	30-60	107.2 (9.1)	89-121
HC	14:16	45.4 (11.5)	25-60	108.8 (6.6)	92-119

Note. M = mean, SD = standard deviation

3.2.2. Age

Participants' ages ranged from 25 to 60 years ($M = 47.5$, $SD = 10.2$). In the MS group, participants were aged between 30 and 60 years ($M = 49.7$, $SD = 8.3$). In the healthy control group, participants were aged between 25 and 60 years ($M = 45.4$, $SD = 11.5$). An independent t-test was used to compare the participants' ages between both groups. Separate variance estimates were used as homogeneity of variance assumptions were not met ($F = 4.12$, $p = .047$). There was no significant difference between the two groups in terms of age ($t(52.67) = 1.67$, $p = .1$). The two groups were therefore matched for age. Consequently, age was not considered in any subsequent analyses.

3.2.3 Estimated Pre-Morbid IQ

The Wechsler Adult Reading Test (WTAR; Holdnack, 2001) was used to estimate participants' pre-morbid Full-Scale intelligence level (FSIQ). Overall, participants' FSIQ scores ranged from to ($M = 108$, $SD = 7.9$). MS participants' scores ranged

from 89 to 121 ($M = 107.2$, $SD = 9.1$). In the healthy control group, scores ranged from 92 to 119 ($M = 108.8$, $SD = 6.6$). Separate variance estimates were used as homogeneity of variance assumptions were not met ($F = 4.69$, $p = .034$). There was no significant difference between the two groups in terms of pre-morbid FSIQ ($t(52.82) = 1.67$, $p = .44$) indicating that the two groups were matched for pre-morbid IQ scores. Consequently, pre-morbid IQ was not considered in any subsequent analyses.

3.2.4. MS Subtypes

The MS sample consisted of five patients with Relapsing Remitting MS (RRMS, 16.7%), ten patients with Primary Progressive MS (PPMS, 33.3%) and fifteen with Secondary Progressive MS (SPMS, 50%).

3.2.5. Fatigue

Independent t-tests were also performed in order to explore potential group differences in self-reported levels of fatigue, anxiety and depression. The Fatigue Severity Scale (FSS) was employed to measure fatigue and the following categories were applied; no fatigue ($FSS < 4$), borderline fatigue ($4 < FSS < 5$) and fatigued ($FSS > 5$). The MS and healthy control groups differed significantly in terms of fatigue ($t(58)=6.81, p<.001$) with MS participants reporting significantly greater levels of fatigue ($M=43.83$, $SD=10.25$) relative to healthy controls ($M=26.1$, $SD=9.92$). The possible influence of this difference in levels of fatigue between the two groups is discussed in later sections.

3.2.6. Depression and Anxiety

Depression and anxiety were measured using the self-report Hospital Anxiety and Depression Scale (HADS). The standard HADS cut-off scores for depression and anxiety include normal (0-7), mild (8-10), moderate (11-14) and severe (15-21) (Zigmond & Snaith, 1983; Bjelland et al., 2002).

Based on these categorisations, 33.3% of participants with MS scored above the cut-off for clinically significant depression (mild (16.7%), moderate (16.7%), severe (0%)), while 66.7% of participants with MS scored in the 'normal' range. Just 10% of the healthy control participants met the criteria for clinically significant depression (mild (6.7%), moderate (3.3%), severe (0%)) while 90% were in the 'normal' range.

Regarding anxiety, 26.7% of participants with MS met the cut-off for clinically significant levels of anxiety (mild (20%), moderate (3.3%) severe (3.3%)), while 73.3% had no significant anxiety symptoms. In the healthy control group, 33.3% demonstrated clinically significant anxiety symptoms (mild (23.3%), moderate (6.7%), severe (3.3%)) while 66.7% were within the 'normal' range.

Independent t-tests revealed a significant difference in levels of self-reported depression between the MS and healthy control groups ($t(58)=5.09$, $p<.001$), with MS participants ($M=6.07$, $SD=3.25$) reporting significantly higher levels of depression relative to healthy control participants ($M=2.47$, $SD=2.7$). There was no significant difference in anxiety levels between the two groups ($t(58)=.56$, $p=.58$), with both the MS ($M=5.33$, $SD=3.59$) and healthy control ($M=5.87$, $SD=3.81$) groups reporting

similar levels of anxiety. The possible influence of this difference in levels of depression between the two groups is discussed in later sections.

3.3. Cognitive Variables

Independent samples t-tests were used to compare both the MS and healthy control group on all but one of the cognitive variables. Scores for both groups on the neuropsychological measures are shown in Table 8. The two groups demonstrated comparable performance on the Verbal Analogies (VESPAR) subtest ($t(58)=1.4$, $p=.166$). The groups differed on the CVLT-II ($t(58)=2.54$, $p=.014$), the SDMT ($t(58)=6.7$, $p<.001$), the Arithmetic ($t(58)=2.79$, $p=.007$), the Verbal Series (VESPAR) ($t(58)=2.3$, $p=.025$) and the TRUSI ($t(57)=3.00$, $p=.004$). The healthy control group performed significantly better than the MS group on each of these five measures. Once Bonferroni corrections were made for the number of comparisons performed, only the difference on the SDMT, Arithmetic and TRUSI variables remained significant ($p<.008$ was taken as the appropriate level of significance). Using the Mann-Whitney U test, it was found that the two groups also performed comparably on the Modified Token Test (MTT) ($U=432.00$, $p=.59$).

Table 8

Summary of the Means, Standard Deviations and Significance Levels for the Cognitive Variables across the MS and Healthy Control Groups

	MS		HC		Significance level
	M (SD)	Range	M (SD)	Range	(<i>p</i> -value)
CVLT-II	55.33 (11.4)	28-74	62.4 (10.12)	39-74	0.014
SDMT	40.73 (9.88)	17-59	57.83 (9.9)	39-81	<0.001*
Arithmetic	9.63 (2.81)	3-17	11.57 (2.56)	8-17	0.007*
Verbal Analogies (VESPAR)	18.43 (2.76)	12-24	19.40 (2.57)	13-23	0.166
Verbal Series (VESPAR)	17.8 (2.57)	14-23	19.47 (3.00)	12-24	0.025
TRUSI	20.59 (6.28)	8-32	24.87 (4.57)	12-32	0.004*
Modified Token Test (non-parametric)	Mean rank = 29.9	13-15	Mean rank = 31.1	14-15	0.59

Note. M = mean, SD = standard deviation, **p*<.008 (following Bonferroni corrections)

3.3.1. Specific Cognitive Impairment

Using a similar procedure to that of earlier studies (e.g. Camp et al., 1999; Camp et al., 2005), a cognitive impairment index was created for each participant using their scores on the CVLT-II, SDMT, Arithmetic (WAIS-III), Verbal Analogies (VESPAR) and Verbal Series (VESPAR) and TRUSI subtests. The mean and standard deviation of the standardisation sample for each measure was employed as a reference (Delis et al., 2000; Langdon & Warrington, 1995; McKnight, 2007; Smith, 1982; Wechsler, 1997) and current MS and healthy control participants' scores were compared with this data for each subtest.

Participants were allocated a grade for each subtest based on the number of standard deviations they fell below the standardised mean. Participants were graded as follows: Grade 0 if they scored at or above the mean, Grade 1 if they scored within one standard deviation below the mean ($<1SD$), Grade 2 if they scored more than one but less than two standard deviations from the mean ($1SD < x < 2SD$), Grade 3 if they scored more than two but less than three standard deviations below the mean ($2SD < x < 3SD$), and so on until all participant scores were graded. The grades for each subtest were then summed to provide one overall score for each participant, indicating their level of cognitive impairment. A higher figure indicated greater cognitive impairment. The cognitive impairment index scores ranged from 0-11 (where 0 indicated no impairment) with a mean score of 4.87 ($SD = 2.89$) in the MS group and 2.63 ($SD = 1.77$) in the control group.

Following the practice of several researchers (e.g. Achiron & Barak, 2003; Camp et al., 1999; Camp et al., 2005, Comi et al., 1995), clinical impairment on any

of the neuropsychological measures was defined as a score of greater than two standard deviations below the mean of the standardisation sample (Delis et al., 2000; Langdon & Warrington, 1995; McKnight, 2007; Smith, 1982; Wechsler, 1997). These researchers typically classified participants as having a more widespread cognitive impairment if they scored more than two standard deviations below the mean on three or more neuropsychological measures (see Table 9).

Table 9

Frequency of Participants Classified as Clinically Impaired (i.e. score of >2 standard deviations below the mean) across all Neuropsychological Measures for the MS and Healthy Control (HC) Group

Measure	MS Group	HC Group
Modified Token Test	0	0
SDMT	9	0
CVLT-II	2	1
Arithmetic (WAIS-III)	1	0
TRUSI	2	0
Verbal Analogies (VESPAR)	0	0
Verbal Series (VESPAR)	0	0

One participant in the MS group scored more than two standard deviations below the mean on three neuropsychological measures, indicating that one MS participant demonstrated more widespread cognitive impairment. No participants in the healthy control group scored more than two standard deviations below the mean on three or more measures.

The Modified Token Test (Coughlan & Warrington, 1978) was used as a screening measure where participants were classified as having an impairment in comprehension if they scored below the clinical cut-off of 12. This is the level at which patients with neurological compromise were distinguished from the healthy

control group in the original sample. No participants scored below this cut-off and thus, all were deemed to have sufficient comprehension ability to complete the full neuropsychological test battery and experimental condition.

3.4. Experimental Condition

3.4.1. Vignette Condition and Presentation Order

Order of presentation condition was counterbalanced across participants to ensure that an equal number of participants in each group (n=10) heard the three different presentation formats (massed, spaced, massed-with-delay) of the three aural risk information vignettes in each presentation order (i.e. (i) ‘massed’ first, ‘spaced’ second and ‘massed-with-delay’ third; (ii) ‘spaced’ first, ‘massed-with-delay’ second and ‘massed’ third; or (iii) ‘massed-with-delay’ first, ‘massed’ second and ‘spaced’ third) (see Table 5 and Abstract 14 for details of randomisation of order of presentation format).

3.4.2. Dependent Variables

The scores for immediate recall of risk information and understanding of risk information across Group (MS and healthy control) and Presentation Condition (massed, spaced, massed-with-delay) are summarised in Table 10 and Table 12 below.

3.4.3. Immediate Recall of Treatment-related Risk Information

A 2 X 3 mixed analysis of variance (ANOVA) with Group (MS and healthy control) as the between-subjects factor and Presentation Condition (massed, spaced, massed-

with-delay) as the within-subjects factor was performed on the immediate recall scores (i.e. percentage correct). There was a significant main effect of Group ($F(1,58)=13.28, p=.001$) indicating that the MS and healthy control groups differed significantly in their ability to immediately recall treatment-related risk information. Mean scores indicate that the healthy control group recalled significantly more risk information relative to MS participants (see Table 10 and Figure 1).

Table 10

Summary of the Descriptive Statistics for Immediate Recall of Risk Information

Scores for MS and Healthy Control Participants across all Conditions

Condition	Group	Mean	Standard Deviation	Range (%)
Massed	MS	22.76	14.91	1.4 - 67.1
	HC	34.1	13.18	12.9 – 57.1
Spaced	MS	28.09	12.74	10 – 55.7
	HC	37.48	16.49	8.6 – 65.7
Massed with delay	MS	14.33	10.37	1.4 – 40
	HC	23.86	10.37	8.6 – 45.7

There was a highly significant main effect of Presentation Condition ($F(2,116)=33.5, p<.001$), indicating that presentation format, either massed, spaced or massed-with-delay, led to significant differences in the amount of risk information which participants were able to recall. Post-hoc t-tests were performed to further investigate this interaction. Paired sample t-tests revealed that participants recalled significantly more risk information in the spaced presentation condition relative to

both the massed presentation ($t(59)=2.32, p=.034$) and massed-with-delay presentation conditions ($t(59)=8.37, p<.001$) (see Table 11). Participants also recalled significantly more risk information in the massed presentation relative to the massed-with-delay presentation condition ($t(59)=5.97, p<.001$). However, once Bonferroni corrections were considered ($p=0.017$), the difference in participants' recall of risk information between the massed presentation and spaced presentation condition was no longer significant.

Table 11

Summary of Post-hoc Analysis Exploring Differences in Immediate Recall Scores between Massed, Spaced and Massed-with-Delay Presentation Conditions

Comparison	Mean	SD	Significance level (<i>p</i>-value)
Massed	28.43	15.08	0.024
V	32.79	15.36	
Spaced			
Spaced	32.79	15.36	<0.001*
V	19.1	11.23	
Massed with delay			
Massed	28.43	15.08	<0.001*
V	19.1	11.23	
Massed with delay			

Note. SD = standard deviation, * $p<.017$ (after Bonferroni corrections)

The interaction between Group and Presentation Condition was not significant ($F(2,116)=.21, p=.82$). While the MS group showed a benefit of spaced presentation for immediate recall of treatment-related risk information, they were not differentially helped by this spaced presentation condition relative to healthy controls, with both groups demonstrating a similar pattern of performance on immediate recall for each presentation condition (massed, spaced, massed-with-delay).

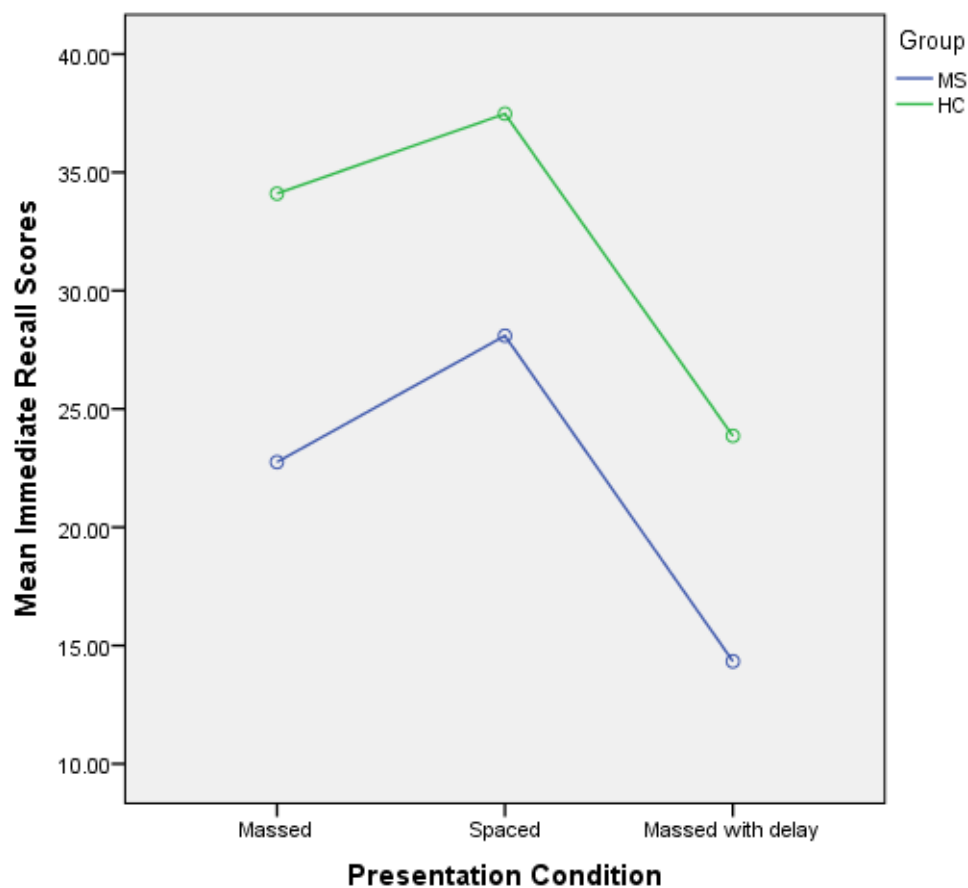


Figure 1. Plot of Immediate Recall of Risk Information Scores for Group and Presentation Condition

3.4.4. Understanding of Treatment-related Risk Information

Another 2 X 3 mixed analysis of variance (ANOVA) was performed on participants' scores on a measure assessing understanding of treatment-related risk information.

Again, Group (MS and healthy control) was the between-subjects factor and Presentation Condition (massed, spaced, massed-with-delay) was the within-subjects factor. This revealed a highly significant main effect of Group ($F(1,58)=14.79$, $p<.001$) indicating that the two groups differed significantly in their ability to make sense of treatment-related risk information. Mean scores indicate that the healthy control group demonstrated a significantly greater understanding of risk information relative to MS participants (see Table 12).

Table 12

Summary of the Descriptive Statistics for Understanding of Risk Information Scores for MS and Healthy Control Participants across all Conditions

Condition	Group	Mean	Standard Deviation	Range (%)
Massed	MS	30.44	20.68	6.3 - 75
	HC	43.97	17.63	6.3 - 75
Spaced	MS	29.18	13.96	6.3 - 62.5
	HC	44.19	20.94	6.3 - 87.5
Massed with delay	MS	28.76	13.69	6.3 - 62.5
	HC	35.43	15.85	6.3 - 75

There was no significant main effect of Presentation Condition ($F(2,116)=1.95$, $p=.15$), with participants demonstrating a similar level of

understanding of risk information across massed, spaced and massed-with-delay information-presentation formats. There was also no significant interaction between Group and Presentation Condition ($F(2,116)=1.22, p=.3$) suggesting that understanding of treatment-related risk information was not differentially affected by any of the three presentation conditions (massed, spaced, massed-with-delay) in the MS and healthy control groups (see Figure 2).

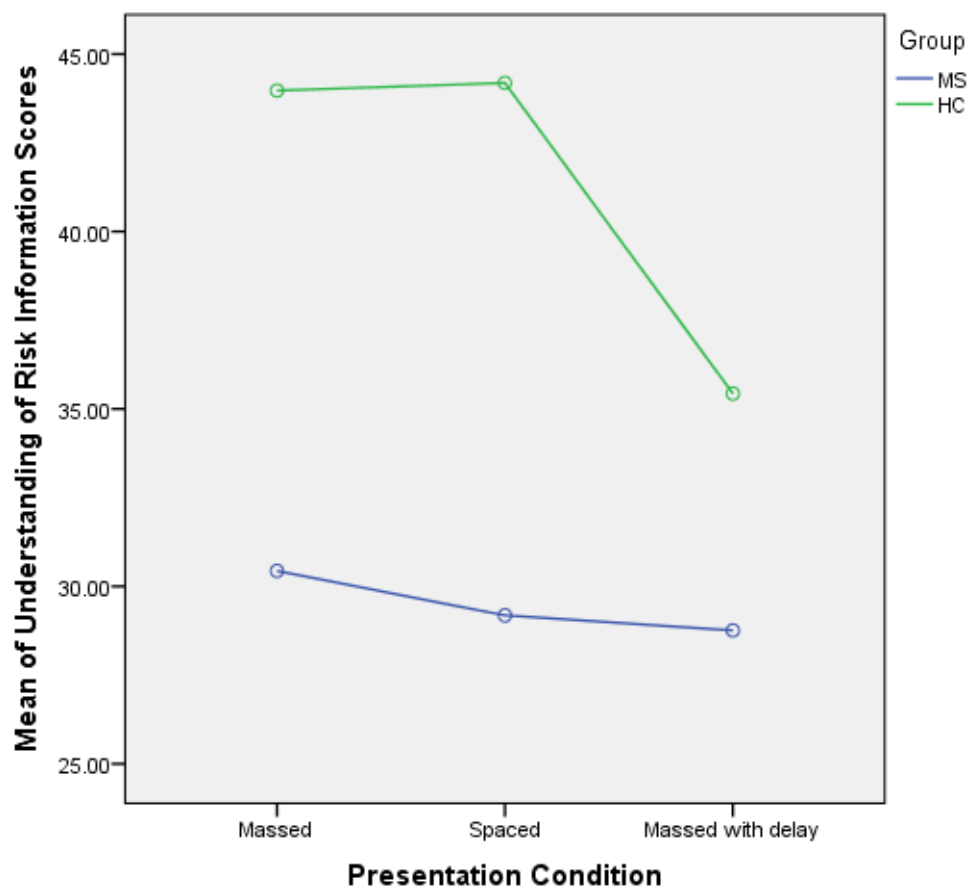


Figure 2. Plot of Understanding of Risk Information Scores for Group and Presentation Condition

3.4.5. Covariance

In order to control for the potential confounding effects of significant group differences, many researchers perform an Analysis of Covariance (ANCOVA). This can establish whether the groups differ on the dependent variable once the effect of other potentially confounding variables are statistically partialled out. However, this is not always appropriate. Despite statistically significant differences between the MS and healthy control groups in levels of self-reported fatigue and depression, an ANCOVA was not performed in the current study. This decision was based on recommendations by Miller and Chapman (2001) who warn against attempts to control for pre-existing, meaningful group differences. This is primarily because the variables of fatigue and depression both represent an inherent difference between the two groups rather than being merely noise or error variance. Thus, entering depression (HADS scores) or fatigue (FSS scores) as covariates would remove meaningful variance from the independent variable (Group) and, in turn, lead to difficulties in interpreting the effect of Group on the dependent variables (immediate recall and understanding of risk information).

The MS and healthy control groups also differed significantly on a measure of information-processing speed (SDMT scores), working memory (Arithmetic subtest scores) and statistical reasoning (TRUSI scores). However, for similar reasons, it was again decided not to enter these variables as covariates in the analysis. The justification for covariate omission will be outlined and evaluated further in the discussion section of this paper.

3.4.6. Cognitive Variables Associated with Immediate Recall and Understanding of Treatment-related Risk Information

In order to explore the associative relationship between each cognitive variable and the dependent variables of immediate recall and understanding of risk information, Pearson correlations were performed. Spearman's rho correlations were performed to explore the relationship between Modified Token Test scores and understanding and recall of risk information in both groups. Each correlation is depicted in Table 13 and Table 14 below. Correlations were calculated for each group separately using the split-file function in SPSS. These correlations were calculated separately for the MS and healthy control groups given that healthy control participants scored significantly higher than MS participants on several of the neuropsychological tests (SDMT, Arithmetic, and TRUSI). This precaution therefore reduced the chance of obtaining artificially inflated correlation coefficients which could have resulted in misleading significant correlations.

3.4.6.1. Cognitive Variables Associated with Immediate Recall of Risk Information in the MS Group

Initial Pearson correlations revealed a significant positive correlation between MS participants' SDMT scores and immediate recall of risk information ($r(28)=.51$, $p=.004$). Therefore, higher scores on the SDMT were associated with higher immediate recall of risk information in the MS group (see Table 13). There was also a highly significant positive correlation between CVLT-II scores and immediate recall of risk information in the MS group ($r(28)=.77$, $p<.001$). This indicates that as verbal memory scores increase, immediate recall scores also increase.

Table 13

Correlations between the Cognitive Variables and the Dependent Variables of Immediate Recall and Understanding of Risk Information in the MS Group

Independent Variable	Immediate Recall of Risk Information		Understanding of Risk Information	
	Pearson Correlation	Significance Level	Pearson Correlation	Significance Level
SDMT	.512**	.004	.536**	.002
CVLT-II	.768**	<.001	.654**	<.001
Arithmetic	.577**	.001	.577**	.001
TRUSI	.582**	.001	.400*	.032
Verbal Analogies (VESPAR)	.649**	<.001	.481**	.007
Verbal Series (VESPAR)	.582**	.001	.374*	.042
MTT (non-parametric)	Spearman's ρ		Spearman's ρ	
	.294	.115	.237	.207

**Correlation significant at the 0.01 level (2-tailed)

*Correlation significant at the 0.05 level (2-tailed)

Another significant positive correlation was observed between MS participants' scores on the Arithmetic subtest of the WAIS-III and immediate recall ($r(28)=.58, p=.001$) and between TRUSI scores and immediate recall ($r(28)=.58, p=.001$). Therefore, better performance on the arithmetic subtest and the TRUSI measure of statistical reasoning respectively were also associated with improved

immediate recall performance in the MS group. The significant positive correlation between MS performance on both verbal analogies ($r(28)=.649$, $p<.001$) and verbal series ($r(28)=.582$, $p=.001$) and immediate recall suggests that higher scores on both of these verbal inductive reasoning measures were also correlated with greater recall of risk information in the MS group. There was no significant correlation observed between scores on the Modified Token Test (MTT) and immediate recall of risk information suggesting that MTT scores were not strongly associated with recall of risk information ($\rho(28)=.29$, $p=.12$).

3.4.6.2. Cognitive Variables Associated with Immediate Recall of Risk Information in the Control Group

Initial Pearson correlations revealed a significant positive correlation between the scores of healthy control participants on the CVLT-II and immediate recall of risk information ($r(28)=.52$, $p=.003$). Therefore, higher scores on the CVLT-II were associated with better performance on a measure of immediate recall of risk information for healthy controls. Further significant positive correlations were observed in the control group between scores on the Arithmetic subtest of the WAIS-III and immediate recall ($r(28)=.43$, $p=.017$), and between TRUSI scores and immediate recall ($r(28)=.46$, $p=.01$). Using a Spearman's rho correlation analysis, a significant positive correlation was also observed between MTT scores and immediate recall ($\rho(28)=.46$, $p=.01$) (see Table 14). Therefore, better performance on the Arithmetic subtest, TRUSI measure of statistical reasoning and MTT respectively were also associated with improved immediate recall performance in the control group. A significant positive correlation was also revealed between scores on both verbal analogies ($r(28)=.518$, $p=.003$) and verbal series ($r(28)=.502$, $p=.005$) subtests

and immediate recall, indicating a relationship between higher verbal and numerical inductive reasoning scores and improved recall of risk information in the healthy control group.

Table 14

Correlations between the Cognitive Variables and the Dependent Variables of Immediate Recall and Understanding of Risk Information in the Healthy Control Group

Independent Variable	Immediate recall of risk information		Understanding of risk information	
	Pearson Correlation	Significance Level	Pearson Correlation	Significance Level
SDMT	.343	.004	.257	.171
CVLT-II	.518**	.064	.276	.14
Arithmetic	.432*	.017	.316	.089
TRUSI	.460*	.01	.176	.354
Verbal Analogies (VESPAR)	.476**	.008	.465**	.010
Verbal Series (VESPAR)	.502**	.005	.319	.085
MTT (non-parametric)	Spearman's ρ		Spearman's ρ	
	.456*	.011	.335	.071

**Correlation significant at the 0.01 level (2-tailed)

*Correlation significant at the 0.05 level (2-tailed)

Interestingly, there was no significant correlation observed between SDMT scores and immediate recall of risk information ($r(28)=.34$, $p=.063$), although this did

approach significance, suggesting that speed of information-processing was not strongly associated with recall of risk information in the control group.

3.4.6.3. Cognitive Variables Associated with Understanding of Risk Information in the MS Group

Pearson correlations were again performed to explore the associations between each cognitive variable and the understanding of risk information (see Table 13 above). These revealed a significant positive correlation between MS participants' SDMT scores and understanding of risk information ($r(28)=.54, p=.003$). Therefore, higher scores on the SDMT were associated with better performance on a measure of understanding of risk information in the MS group. There was also a highly significant positive correlation between CVLT-II scores and the understanding of risk information in the MS group ($r(28)=.65, p<.001$). This indicates that increased verbal memory scores were associated with increased understanding of risk information.

Another significant positive correlation was observed between MS participants' scores on the Arithmetic subtest of the WAIS-III and understanding of risk information ($r(28)=.58, p=.001$) and between TRUSI scores and understanding of risk information ($r(28)=.4, p=.032$). Therefore, better performance on the Arithmetic subtest and the TRUSI measure of statistical reasoning respectively were also associated with improved understanding of risk information in the MS group. A significant positive correlation between scores on both verbal analogies ($r(28)=.481, p=.007$) and verbal series ($r(28)=.374, p=.042$) subtests and understanding of risk information was also revealed, suggesting that higher scores on both of these verbal

inductive reasoning measures was also correlated with greater comprehension of risk information in the MS group.

There was no significant correlation observed between scores on the Modified Token Test (MTT) and understanding of risk information suggesting that MTT scores were not strongly associated with understanding of risk information ($\rho(28)=.24$, $p=.21$).

3.4.6.4. Cognitive Variables Associated with Understanding of Risk Information in the Control Group

Only one significant correlation was observed between the scores of healthy control participants on any of the cognitive variables and the understanding of risk information (see Table 14 above), that of verbal analogy (VESPAR) scores ($r(28)=.465$, $p=.01$). The correlation between the other verbal inductive reasoning test (Verbal Series) approached significance ($r(28)=.319$, $p=.085$). A positive correlation between the understanding of risk information and both Arithmetic scores ($r(28)=.32$, $p=.089$) and MTT scores ($\rho(28)=.31$, $p=.071$) did also approach significance. Overall, this suggests that understanding of risk information in the healthy control group was positively associated with verbal reasoning ability, albeit not consistently, but was not significantly associated with performance on measures of information-processing speed (SDMT), immediate verbal recall (CVLT-II), verbal comprehension (MTT), working memory (Arithmetic subtest) or statistical reasoning ability (TRUSI).

3.4.6.5. Association between the Cognitive Impairment Index Scores and Immediate Recall and Understanding of Treatment-Related Risk Information

Pearson correlations were also conducted to explore the relationship between the cognitive impairment index scores and the dependent variables of immediate recall and understanding of risk information. Again, this was calculated separately for each group (see Table 15).

Table 15

Pearson r Correlations for the Association between Cognitive Impairment Index Scores and the Dependent Variables of Immediate Recall and Understanding of Risk Information in the MS and Healthy Control (HC) Groups

		Immediate Recall of Risk Information		Understanding of Risk Information	
Cognitive Impairment Index Scores		Pearson Correlation	Significance Level	Pearson Correlation	Significance Level
	MS	-.706**	<.001	-.665**	<.001
	HC	-.593**	.001	-.482**	.007

**Correlation significant at the 0.01 level (2-tailed)

These analyses revealed a highly significant negative correlation between cognitive impairment index scores and immediate recall of risk information ($r(28)=-.706$, $p<.001$) and understanding of risk information ($r(28)=-.665$, $p<.001$) in the MS group. The same highly significant negative correlation was also observed between cognitive impairment index scores and immediate recall ($r(28)=-.593$, $p=.001$) and understanding ($r(28)=-.482$, $p=.007$) of risk information in the healthy control

group. Therefore, cognitive impairment scores were associated with both immediate recall and understanding of treatment-related information in both groups, with higher cognitive impairment scores being linked to reduced recall and understanding.

4. Discussion

It has recently been suggested that the spaced presentation of information can improve recall in the MS population during simple laboratory-based tasks (Goverover et al., 2009b; 2011). The current study aimed to explore whether spaced presentation of information could improve both recall and understanding of information in people with MS in a more clinically-relevant context, using treatment-related risk information. This study addressed the following questions: Does spaced presentation of treatment-related risk information facilitate improved recall and understanding of risk information? Are people with MS differentially affected by spaced presentation of treatment-related risk information relative to healthy controls? The specific cognitive functions associated with recall and understanding of treatment-related risk information were also explored.

4.1. Review of the Findings

4.1.1. Hypothesis 1

The MS group will understand and recall significantly less treatment-related risk information relative to a healthy control group.

This hypothesis was supported. Participants with MS performed significantly worse than healthy controls on measures of both immediate recall and understanding of treatment-related risk information. As the groups were matched for age, gender and pre-morbid IQ, these differences in performance cannot be attributed to age-related cognitive changes, gender-related cognitive differences, or pre-existing differences in level of general intellectual function respectively.

The groups did differ significantly in self-reported levels of fatigue and depression, with the MS group experiencing higher levels for both variables. Research into the effects of fatigue and depression on cognitive performance in MS have provided mixed results, with some studies demonstrating significant associations between reduced cognitive performance and depression (Arnett, Higginson, & Randolph, 2001; Demaree, Gaudino, & DeLuca, 2003; Diamond et al., 2008) or chronic fatigue (Diamond et al., 2008; Krupp & Elkins, 2000;) in MS samples. However, other studies report no significant association between cognitive function and fatigue (Bailey et al., 2007; Parmenter et al., 2003) or depression in MS (Karadayi et al., 2014). In any case, it was not possible to explore the influence of fatigue or depression on cognitive function within the present study as it would have reduced power had either fatigue or depression been entered as a covariate in the analyses. Both fatigue and depression are known to be more prevalent in people with MS relative to healthy controls (e.g. Bol et al., 2009; Goldman Consensus Group, 2005; Sundgren et al., 2013) and this difference reflects a real clinical circumstance and common co-morbidity. Therefore, co-varying these two variables would have removed meaningful variance from the independent variable of Group and led to potentially spurious findings (Miller & Chapman, 2001).

There were also significant differences between the MS and healthy control groups in their performance on a number of neuropsychological measures including a test of information-processing speed, working memory and statistical reasoning. The MS group demonstrated reduced performance on each of these tasks. However, previous research has rather consistently documented MS-related impairments in information-processing speed (Bodling, Denney & Lynch, 2012; Denney, Gallagher

& Lynch, 2011; Drake et al., 2010), working memory (Legenfelder, Chiaravalloti, Ricker & DeLuca, 2003) and, to a lesser extent, statistical reasoning (McKnight, 2007). Again then, given that the significant difference in performance on these tasks likely reflects an inherent, meaningful difference between the two groups, it was decided not to include these cognitive variables as covariates in the analysis. Instead, the cognitive correlates of immediate recall and understanding of risk information were later explored. (This is discussed in section 4.1.4).

4.1.2. Hypothesis 2

The spaced presentation of treatment-related risk information will significantly improve recall and understanding of risk information in both MS and healthy control participants relative to massed presentation of information.

This hypothesis was partially supported. Participants recalled a significantly greater amount of treatment-related risk information when the presentation of this information was interspersed with breaks (spaced presentation) relative to continuous presentation (massed presentation). Once Bonferroni adjustments were applied for the number of comparisons made, this finding approached significance and a larger sample size may have provided more power to maintain a significant effect.

Nonetheless a strong trend for a benefit of spaced presentation on recall was observed.

Participants also recalled significantly more risk information in the massed condition relative to the massed-with-delay condition, and in the spaced presentation relative to the massed-with-delay condition and these findings remained significant once Bonferroni corrections had been made. This finding of improved recall in the massed relative to the massed-with-delay condition is not surprising given that

participants either recalled the information immediately or had to wait for 10-minutes before recall and it is widely documented that recall declines even after several minutes delay (Cowan & AuBuchon, 2008; Oberauer & Lewandowsky, 2009).

The finding of significantly greater recall of risk information in the spaced relative to the massed-with-delay condition is, however, a novel one and partially supports the hypothesis that there would be a benefit of spaced presentation of risk information. The ‘massed with 10-minute-delay’ condition was included to prevent an otherwise significant benefit of spaced presentation for recall being confounded by the time delay (2 X 5 minutes) between participants hearing the first and final sections of the drug extract in this spaced presentation condition. The finding of significantly greater recall of risk information in the spaced presentation relative to the massed-with-delay condition, where both involve a similar time-delay, thus suggests that these breaks/spaces in information presentation afford some benefit over continuous presentation of information.

Overall then, the present study provides some support for the advantages of information-presentation interspersed with breaks in enhancing immediate recall of risk information. This study did not find evidence for a similar benefit of spaced presentation in facilitating improved understanding of risk information. Participants’ level of comprehension of treatment-related risk information did not differ greatly whether the information was presented in a continuous or spaced format.

4.1.3. Hypothesis 3

There will be a greater benefit of spaced presentation of risk information in the MS group relative to a healthy control group.

This hypothesis was not supported. As expected, both groups demonstrated a benefit of spaced presentation for immediate recall of risk information. However, it was hypothesised that the MS group would demonstrate a significantly greater benefit from a spaced information presentation style due to their well-documented impairments in speed of information-processing (e.g. Bodling et al., 2012; Chiaravalloti et al., 2013; Denney et al., 2011) and the potential for spacing to ameliorate this by providing more processing time. Instead, both groups demonstrated a similar pattern of performance for immediate recall across the different presentation conditions (massed, spaced, massed-with-delay).

As mentioned above, there was no evidence to suggest that the spacing of information improves understanding of treatment-related risk information when compared with continuous presentation. Furthermore, both groups demonstrated a similar pattern of performance on a measure of understanding of risk information for each presentation condition (massed, spaced, massed-with-delay). This suggests that whether risk information is presented continuously or in a spaced format does not affect participants overall comprehension of risk information, regardless of whether they have MS or not.

4.1.4. Hypothesis 4

Reduced speed of information processing will be associated with reduced recall and understanding of treatment-related risk information.

This hypothesis was partially supported. Performance on the SDMT, a test of information-processing speed, was associated with both immediate recall and understanding of treatment-related risk information in the MS group. As expected, this relationship was positive, with reduced information-processing speed being linked to poorer recall and understanding of risk information in this group. However, in the healthy control group, SDMT performance was the only cognitive variable not significantly related to immediate recall of risk information. Moreover, information-processing speed was also not related to understanding of risk information in the control group. This may be because the range of SDMT scores in the healthy control group was too restricted to detect a significant correlation, with little spread of scores around the mean on this variable.

Other cognitive correlates of risk awareness were also explored. Interestingly, in the MS group, only comprehension of risk information (i.e. scores on MTT) did not correlate with either recall or understanding of this information in this experiment. In the healthy control group, performance on a measure of comprehension (MTT) did correlate with recall of risk information. However, like the MS group, it was not associated with understanding of risk information. This is a relatively simple measure of comprehension for which the majority of participants were at ceiling level. Again then, lack of variability in MTT scores in either group likely reduced the likelihood of

observing a significant correlation between comprehension and risk awareness. This is discussed further in section 4.2.4.

Finally, in the healthy control group, only one of two verbal reasoning tasks correlated with understanding of risk information, although three other variables did approach significance (working memory, a numerical reasoning task, and comprehension). Notably however, the MS group performed significantly worse on five of the seven neuropsychological measures, although just three of these differences remained significant once adjustments were made for the number of group comparisons. This suggests that a relationship between risk awareness, in particular comprehension of risk information and these numerous cognitive functions, only becomes apparent in the context of cognitive deficits. A small spread of scores around the mean for these test scores in the control group is again likely to at least partly explain the present findings. (This is discussed further in section 4.2.4.)

4.2. Interpretation

4.2.1. The MS group demonstrated significantly lower treatment-related risk awareness (recall and understanding of risk information) when compared with a healthy control group.

The finding of reduced recall of risk information in MS relative to a healthy control sample replicates results from many earlier studies (for review see section 1.4.2) which find that MS participants require a greater number of learning trials in order to perform at a similar level to healthy control participants on a number of verbal recall tasks (e.g. DeLuca et al., 1998; Demaree et al., 2000; Gaudino et al., 2001; Lafosse et al., 2013). This verbal recall deficit is thought to be due to reduced information-

processing speed in MS which impacts on acquisition of verbal information by limiting the amount of information which can be encoded and processed for storage in long-term memory (Chiaravalloti et al., 2013).

Reduced risk awareness in MS has also been documented by several previous studies. In relation to treatment-related risk, individuals with MS have previously been shown to underestimate the risk of experiencing severe treatment-related side effects such as cardiotoxicity or leukaemia (e.g. Hoffman et al., 2012) while overestimating treatment benefits (e.g. Hessen et al., 2010a). Certainly, reduced risk awareness in the general population is well-documented and thought to be due in large part to poor numeracy rates (Elwyn et al., 2012; Reyna et al., 2009) occurring across all educational backgrounds (Lipkus et al., 2001). These involve both underestimation (e.g. Knauper et al., 2005) and, less often, overestimations (e.g. Fuller et al., 2004) of the risk of experiencing negative side-effects resulting from a particular medication or lifestyle pattern. However, MS-specific studies suggest that reduced risk awareness in this group is more complex than this one factor of low numeracy levels. It is not unreasonable to assume that well-documented cognitive deficits in MS may further impede adequate risk awareness in MS, over and above that of low numeracy. Unfortunately, studies specifically addressing this are lacking.

Only one study, to this author's knowledge, directly explores the impact of MS-related cognitive difficulties on the understanding of treatment-related risk information. This study revealed that MS participants with cognitive deficits demonstrated poorer understanding of treatment information when compared with both a control group and an MS group without cognitive deficits. Furthermore, this reduced understanding of treatment-related information was associated with MS-

related impairments in new learning and executive function (Basso et al., 2010). The present study provides some further evidence of reduced understanding of risk information in MS. Studies in a number of other patient groups have found that reduced ability to understand information about diagnoses and the risks and benefits of treatment options is most commonly associated with greater cognitive impairment (Dunn et al., 2006; Palmer & Salva, 2007) and so one might expect that MS-related cognitive impairments are no different in terms of their impact on comprehension of risk information.

The present study provides some further tentative support for the assumption that MS-related cognitive deficits are associated with reduced risk awareness in MS by demonstrating that individuals with MS perform significantly worse than healthy controls on measures assessing recall and understanding of risk information. Since a degree of low numeracy would be expected in both the healthy control and MS group based on its relative frequency in the general population, this finding provides a sense of the impact of MS-related difficulties on risk awareness largely separate from numeracy ability. Moreover, it was clear from results on the TRUSI that the MS group had significantly poorer statistical reasoning ability relative to controls. It was not possible for this study to directly say whether this was a result of MS-related impairments but given that both groups were matched on pre-morbid IQ, it is possible that this was the case. Therefore, the present study somewhat informally suggests that MS-related cognitive deficits may contribute to the reduced risk awareness observed in the MS group.

4.2.2. The spaced presentation of treatment-related risk information improved recall of risk information in both the MS and healthy control group relative to

massed presentation but did not improve understanding of risk information in either group.

This study replicates the findings from the two studies which have previously shown that spaced presentation of information improves recall in MS (Goverover et al., 2009b; Goverover et al., 2011). These studies found that spacing out learning trials on paragraph learning or functional tasks (learning names, appointment times or object locations) led to significantly greater recall of this information when compared with performance following continuous presentation of the same material. They thus concluded that presenting information in chunks over time facilitates better verbal learning and memory in MS. These studies were however limited in that they possessed little ecological validity. Paragraph learning tasks, for example, typically comprise simple stories that have no personal meaning for the individual. The same can be said for name-learning trials. This makes these findings difficult to generalise to more meaningful and complex everyday situations facing individuals with MS.

The present study was able to overcome this limitation by using realistic risk-benefit treatment information, similar to that often presented to patients with MS in clinical settings. In doing so, this more ecologically valid study demonstrated that the benefits of presenting information in a spaced format, interspersed with breaks, hold true in MS even in the case of memory for complex, meaningful and highly relevant information. Thus, learning and recall of risk information in MS is facilitated by the distribution of learning trials over time and these effects may be generalised to MS clinical settings to aid the recall of risk-benefit information for different medication options.

Moreover, the present study was the first to separate out the effects of spaced presentation on recall from that of repetition in MS. Goverover and colleagues' (2009b; 2011) had not done so. In the spaced condition, their task was presented in full and repeated after 5-minute intervals. In the massed condition, their task was presented consecutively three times. Yet, other studies have documented a benefit of repetition alone for recall in MS (e.g. DeLuca et al., 1998; DeLuca et al., 2013). In the present study, extracts in the spaced condition were presented in three separate segments with each heard just once. The findings show that spaced presentation can improve recall of risk information in MS, independent from any benefit of repetition, thus strengthening the support for a benefit of spaced presentation on recall in MS.

In contrast to verbal recall memory in MS, no studies, to this author's knowledge, had previously explored the benefit of spaced presentation for understanding of information in MS. Due to the more ecologically valid nature of the present study, using aurally-presented complex and meaningful medication-related information rather than simple paragraph or name learning tasks, it was more feasible to also test understanding of risk information in MS. However, the present study did not find any evidence to support the hypothesis that presenting information over time and interspersed with breaks would facilitate greater understanding of risk information in either the MS or healthy control group. Thus, it can be concluded that spaced presentation of treatment-related risk information can improve participants' ability to recall this complex information but does not improve their ability to comprehend this information.

There are many possible reasons as to why the spacing effect seems not to improve understanding of treatment-related risk information in either group. Firstly,

the information presented is highly complex, containing multiple forms of statistical and numerical information (e.g. percentages, frequencies, risk-benefit ratios) that are difficult for people to comprehend (Peters, 2012; Reyna et al., 2009). Providing greater time to process this complex information may be sufficient to improve recall but is unlikely to help individuals overcome a more fundamental difficulty in statistical reasoning.

Secondly, comprehension of risk information is likely to involve the interaction of a number of cognitive abilities, and in this way, is a more complex and higher-order cognitive function when compared to verbal recall. Understanding risk information likely relies to some degree on memory, verbal reasoning and arithmetic ability in order to calculate one's personal risk, statistical reasoning in order to infer meaning from these calculations, and executive functions such as identifying, planning and organising key pieces of information (Peters et al., 2007). As such, improving recall of risk information by using spaced presentation may only be addressing one of several key components necessary for successful comprehension of risk information. Further alterations in the way information is presented are therefore required to improve understanding of risk information in MS and other groups.

One strategy may be to alter the syntax, or structure, of information extracts. One study asked patients facing abdominal surgery to describe their illness and treatment in their own words. They found that using patient-worded information led to greater comprehension of illness and treatment information when compared with doctor-developed information and this patient-worded information was better understood across a range of educational levels (Kusec et al., 2006). This study

recommends greater service user involvement in the development of treatment-related information and this may also be of benefit in MS clinic settings.

Altering the type of statistical information provided may also help.

Consistency in the types of numerical formats used is important when presenting statistical information about risks, for example, comparing percentages with percentages rather than percentages with frequencies (Lipkus, 2007). Many researchers (e.g. Lipkus, 2007; Garcia-Retamero, Okan, & Cokely, 2012) also advocate the use of visual aids (e.g. graphs, bar charts) in conjunction with numerical risk information when depicting levels of risk, something which was not afforded in the present study. Finally, studies of different patient populations recommend that clinicians employ an interactive communication strategy in order to improve both participants' recall and comprehension of health-related information (e.g. Kripalani & Weiss, 2006; Schillinger et al., 2003). This strategy involves clinicians assessing patients' recall and understanding of new information presented in clinic, also known as the 'teach-back' method.

4.2.3. Both the MS and Healthy Control groups demonstrated an equal benefit of spaced presentation on immediate recall of risk information.

It was hypothesised that the MS group would demonstrate a greater benefit of spaced presentation for recall of risk information because of the expected deficit in speed of information-processing within this group. Owing to this deficit, it was felt that participants with MS may have more to gain from regular breaks during the presentation of information. Although the MS group was found to have significantly reduced information-processing speed relative to the control group, this did not

translate into a greater improvement in recall of risk information following spaced presentation when compared to control participants.

While the hypothesis was not supported, this finding is in line with previous studies which also report equal benefit of spaced presentation for recall on a paragraph learning task (Goverover et al., 2009b) and name-learning task (Goverover et al., 2011) in MS and healthy control groups. In these studies, the MS group also performed significantly worse than the control group on a measure of information-processing speed. However, the current study is similar to these earlier studies in that not all participants with MS demonstrated reduced performance on the SDMT. Hence, as was similarly suggested by Goverover and colleagues (2011), a future study using a group of participants with MS, all of whom demonstrate reduced information-processing speed, may reveal a greater benefit of spaced presentation on recall of risk information in people with MS relative to healthy controls.

It may also be that there is an optimum break time that ensures greatest compensation for information-processing speed impairments, above or below which the benefit of spaced presentation for recall in people with MS may decline. Moreover, the optimum timing of spaces may vary depending on the amount and complexity of risk information provided. It has been shown that as cognitive load increases, the difference in performance on information-processing speed tests between MS and control groups also increases (e.g. Denney et al., 2011; Paramenter et al., 2007; Reicker et al., 2007). The current study provides complex treatment-related risk information which is much more cognitively demanding in nature than that conveyed in the simple paragraph or name learning tasks of previous studies. Thus, one could expect greater compensation to occur if an optimum break time was

employed in the spaced condition. This may then have resulted in significantly greater benefit of spacing in MS relative to control groups. Further studies could explore different time lengths of the breaks or ‘spaces’ provided in spaced presentation conditions, during which time an additional benefit for the MS group may be found.

4.2.4. Reduced speed of information-processing was associated with reduced recall and understanding of treatment-related risk information in the MS group only, while comprehension did not correlate with either recall or understanding of risk information.

Reduced speed of information-processing was associated with reduced risk awareness in the MS group. This is the first study to document this relationship in MS. While many studies demonstrate reduced recall in MS and attribute this largely to a deficit in information acquisition associated with reduced processing time (e.g. Arnett, 2004; Chiaravalloti et al., 2013; DeLuca et al., 1994; Lafosse et al., 2013), only a limited number have directly measured the association between information-processing speed and recall of information. These few studies reveal positive correlations between verbal recall and information-processing speed in MS (e.g. DeLuca et al., 1994; Diamond et al., 2008) and one recent study reported information-processing speed to be the strongest predictor of new learning ability in MS (Chiaravalloti et al., 2013).

Notably, these previous studies found an association between information-processing speed and recall in MS in the context of simple laboratory-based tasks (e.g. word-list learning, paragraph or story learning) which possess little relevance or meaning and limited generalisability to everyday or clinical encounters. Furthermore, none, to this author’s knowledge, have directly explored the association between

information-processing speed and the understanding of information in an MS population. The present study therefore goes a step further by providing evidence of the benefits of spaced presentation for recall even in the context of more complex, ecologically valid and clinically-relevant information, namely treatment-related risk information. It also directly explores the association between information-processing speed and the understanding of information in MS.

Only one previous study had alluded to a relationship between understanding of risk information and information-processing speed in MS. A significant inverse association between information-processing speed deficits in MS and capacity to make risk-based decisions was reported (Farez et al., 2014). Participants with MS who scored lower on a test of information-processing speed (SDMT) were more likely to make high-risk decisions. However, understanding is just one of four key components (understanding, reasoning, appreciation, expression; Grisso et al., 1997) thought to relate to decision-making capacity, and so this earlier study did not directly highlight the link between understanding of risk information and processing speed.

In contrast to the MS group in the present study, speed of information-processing did not correlate with risk awareness in the healthy control group. Healthy control participants performed significantly better than participants with MS on the SDMT and, unlike participants with MS, all scored within the normal range on this measure. Unsurprisingly then, there was much less variability in this group relative to the MS group, with very little spread of scores around the mean. Given that control group participants were not impaired on this variable, it is perhaps not surprising that their recall and understanding of treatment-related risk information was not associated with information-processing speed.

Comprehension, as measured by performance on the Modified Token Test (MTT), was the only cognitive function not associated with either recall or understanding of treatment-related risk information in the MS group. It was also only correlated with recall of risk information in the control group. This is a rather simple test in which all participants, whether in the MS or control group, performed within the normal range. In fact, most participants were at ceiling level, scoring 15/15. The purpose of this test in the present study was more as a screening measure than an optimum measure of comprehension ability. As such, it ensured that participants' level of comprehension was sufficient to proceed with the full experimental test but it did not capture potentially significant group differences or within-group variability in comprehension levels. Therefore, it is not surprising that comprehension did not typically correlate with risk awareness in this study. Furthermore, verbal comprehension has been shown to be intact in people with MS (Clemmons et al., 2004; Drew, et al., 2008; Prakash, et al., 2008; Ryan et al., 2012) and so it was not expected that there would be a significant correlation between comprehension and recall or understanding of risk information in this group.

However, the cognitive impairment index scores correlated strongly with both the understanding and recall of risk information in both the MS and healthy control groups. Thus, overall cognitive performance was associated with understanding and recall of risk information, where greater cognitive function was linked to better risk awareness in both groups.

4.3. Limitations of the Study

4.3.1. Neuropsychological Tests Completed During Presentation Breaks

Participants completed neuropsychological tests during the breaks of the spaced presentation condition and during the 10-minute break of the massed-with-delay condition. This was primarily due to the lengthy nature of the full test battery and was aimed at limiting the time burden and fatigue experienced by participants. Yet a vast number of studies provide evidence for memory decay over time (e.g. Cowan & AuBuchon, 2008; Portrat, Barrouillet & Camos, 2008), which many attribute to interference and distraction which prevents rehearsal of the new information (e.g. Fernandes & Moscovitch, 2000; Oberauer & Lewandowsky, 2009). Consequently, the administration of these neuropsychological tests may have increased task difficulty making it more difficult to later recall and comprehend the treatment-related risk information in the spaced and massed-with-delay conditions. Hence, this may have reduced the likelihood of observing a significant benefit of spaced presentation relative to massed presentation in improving risk awareness. Nonetheless, a significant benefit of spaced presentation relative to massed presentation was still observed for recall, although this only approached significance once Bonferroni corrections were made. Perhaps a stronger benefit of spaced presentation for recall would have been observed had participants not completed neuropsychological tests in any of the presentation conditions.

Moreover, the tests administered in the spaced presentation breaks (WTAR and SDMT) and 10-minute delay period (Arithmetic subtest) were consistent across all participants. Therefore, one could argue that the inclusion of neuropsychological measures in break periods was unlikely to have influenced findings of group differences in recall and understanding of risk information. Conversely, research has also shown that memory decay may be more pronounced in MS relative to healthy

control participants with greater susceptibility to interference and distraction in this group (e.g. Diamond, DeLuca, Kim, & Lee, 1996; Johnson, DeLuca, Diamond, & Natelson, 1998; Griffiths et al., 2005). Thus, the interference caused by the administration of neuropsychological tasks may be a potential confound, possibly inflating the observed group differences in risk awareness.

4.3.2. Ecological Validity of the Experimental Tasks

The three fictitious treatment-related vignettes, as well as the measure of understanding of risk information for each vignette, were developed specifically for this study. As such, there is no established validity or reliability for the vignettes or the measures of recall and understanding used. In terms of vignette development, review of the vignettes by a number of MS consultants and MS nurses who work within MS clinics and who regularly provide treatment-related information to MS patients may have provided valuable feedback prior to the beginning of this study in terms of ecological validity and use of appropriate language and statistics. While outside the scope of the present study, it would also be possible to correlate the fictitious vignettes with information provided in a clinical context. However, the scoring method applied for immediate recall in the present study was based on the scoring method used by several well-established neuropsychological tests of verbal memory, for example the BMIPB (Coughlan et al., 2007). Moreover, the measure used to assess understanding of risk information was designed to capture participants' understanding of numerical and verbal risk information and was scored in a way similar to some well-established measures of comprehension (e.g. Comprehension subtest of the WAIS-III where participants also receive 0-2 points depending on whether their response is correct, partially correct or incorrect; Wechsler, 1997a).

Furthermore, every effort was made to ensure that the type of information presented emulated that typically provided in MS clinics (e.g. style, wording, format of statistical information), although the similarity to real-world examples has not been formally tested. Nevertheless, it is typical for information provided in clinic to vary based on many factors such as clinician's communication style (e.g. Robinson, 2002) or format of presentation (e.g. verbal, written, visual) and so some variability in presentation is natural.

It could be argued that the use of non-MS relevant treatment-related risk information may have reduced the ecological validity and generalisability of the current findings. Based on previous research which documents increased recall for more meaningful stimuli (e.g. Barense, Henson, & Graham, 2011; Janiszewski et al., 2003), it may be that greater meaning and relevance of MS treatment information may have led to a greater benefit of spaced presentation for recall in the MS group relative to healthy controls. However, the inclusion of MS-specific treatment-related risk information may also have introduced further potentially confounding factors which might impact on risk awareness, for example increased anxiety among patients with MS following the presentation of prognosis and treatment information (Kessels, 2003) or greater prior knowledge of the risk-benefit profiles in participants with MS relative to controls. Furthermore, MS-specific information would have been biased in favour of the MS group as it would have been more meaningful for people with MS and would therefore have unfairly disadvantaged the control group. Using realistic but neutral treatment-related risk information arguably provided a more accurate sense of the group differences in risk awareness and also the relative benefits of spaced presentation for each group, aspects which were of primary interest in this study.

It has also been discussed in earlier sections how the effects of depression and anxiety on cognitive performance remain unclear with both significant and non-significant correlations reported between both anxiety and depression and cognitive function (e.g. Diamond et al., 2008; Karadayi et al., 2014). In the current study, it was not expected that the MS group would have had a significantly greater number of emotional barriers to processing, recalling and understanding the presented treatment-related risk information when compared with healthy control participants. Firstly, while the MS group self-reported higher levels of depression, both groups reported similar levels of anxiety. Secondly, non-MS related information was employed and the three fictitious vignettes instead comprised realistic, non-MS specific treatment information. As mentioned above, this was chosen in part to reduce the potential confound of greater emotional barriers in the MS group when processing information relevant to their condition. Finally, observations and conversations with participants revealed that test anxiety featured in both groups for a small number of participants and numerous members of both groups had endured significant health difficulties in the past (e.g. cancer) which could potentially increase anxiety in either group on hearing health-related information. Overall then, it was not felt that emotional barriers to the processing of risk information would have confounded findings of group differences in aspects of risk awareness within the current study.

Anecdotally, some participants reported that they typically write down information in clinic or bring a spouse or relative along to help them recall and weigh up treatment-related and prognostic information. For many participants with MS then, the current experimental task possessed some notable differences to their typical clinic visit. However, the use of a verbal recall measure and the lack of external

memory aids in the current study were arguably a better method of exploring group differences in risk awareness and to get a baseline measure of the potential benefit of spaced presentation for risk awareness. Furthermore, some participants with MS were no longer able to write well and several relied on carers rather than relatives or friends. Of course, spaced presentation is just one of several ways of improving risk awareness in MS and, where possible, writing down clinic information or bringing along an accompanying relative or friend, are also likely to benefit risk awareness in many cases.

Again, while not being within the scope of this study, a more detailed assessment of risk understanding in MS could have provided further much-needed insight into comprehension level in this patient group. Specifically, it would be interesting to know whether participants with MS tended to overestimate or underestimate risks. Of the few studies which document reduced risk awareness in MS, most reveal a tendency for patients to overestimate treatment benefits (Heesen et al., 2010a) and underestimate severe treatment side effects (Hoffman et al., 2012). Moreover, a multiple choice question format (perhaps offered if participants initially failed to provide the correct response) may have helped assess whether patients with MS could respond correctly with support. This in turn might indicate whether they can demonstrate improved understanding once memory has been prompted using the options provided. In this way, it might also disentangle recall from the other elements involved in understanding risk information, for example planning and organising elements of the presented information.

4.3.3. Choice of Neuropsychological and Clinical Measures

No significant correlation was found between comprehension and either understanding or recall of risk information in the MS group. Comprehension also did not correlate with understanding of risk information in the healthy control group. However, comprehension was measured using the Modified Token Test (MTT) which, as discussed above, has a low ceiling and was included more as a screening measure to ensure a basic level of comprehension in the sample. Perhaps another more complex measure of comprehension could have been employed, for example the Comprehension or Information subtests of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997a; or WAIS-IV; Wechsler, 2008). This may have resulted in more variability within and between the groups and provided a more accurate account of the relationship between comprehension and risk awareness.

The neuropsychological test battery assessed several cognitive domains thought to be most relevant to recall and understanding of treatment-related risk information, the variables central to the present study. A more extensive neuropsychological battery was not deemed possible given the time-constraints for completion of the study and the need to both reduce the impact of fatigue on MS participants and to encourage study participation by both MS and healthy controls, many of whom obliged to participate despite working full-time. Therefore, several important cognitive functions were not assessed. Most notably, executive function was not assessed. Measures from the DKEFS battery (Delis et al., 2001) such as the Tower of London or the Colour-Word Interference subtests could have assessed abilities such as planning, problem-solving and inhibition. Individual tests such as the Stroop Colour-Word Test (Stroop, 1935), Wisconsin Card Sorting Test (WCST; Berg,

1948) or The Brixton Spatial Anticipation Test (Burgess & Shallice, 1997) would also have provided information on inhibition, problem-solving and planning abilities respectively. These abilities may be correlated with understanding of complex risk information in that a deficit in one or several domains of executive function may reduce one's ability to adequately identify, organise and sort key pieces of risk information or to inhibit less relevant information. Indeed, studies of risk awareness and decision-making in other neurological conditions, such as Parkinson's Disease and dementia, have documented a correlation between understanding of risk information and performance on tests of executive function. Furthermore, one test of understanding of risk information in MS found a significant positive correlation between executive function and understanding of risk information, whereby reduced performance on the WCST was associated with reduced understanding of risk (Basso et al., 2010).

The inclusion of measures of complex attention may also have provided further insight into possible correlates of understanding of risk information, particularly in the MS group. Furthermore, tests of narrative memory rather than the word-list learning verbal memory task (CVLT-II) may have added merit to the study. The first five recall trials of the CVLT-II have well-established validity and reliability in screening for verbal learning difficulties in MS (Langdon et al., 2012) and are commonly used to assess verbal recall in clinical and research settings. However, narrative based measures such as the Story recall subtest of the BIRT Memory and Information Processing Battery (BMIPB; Coughlan et al., 2007) or Logical Memory subtest of the Wechsler Memory Scale (WMS-III UK; Wechsler, 1997b; WMS-IV UK; Wechsler 2009) are more similar in nature to the experimental task, affording

more ecological validity, and may have thus been correlated with the experimental task.

In regards to the clinical measures, it may also have been worthwhile to include a measure of adaptive functioning. While severity of fatigue was assessed using a self-report questionnaire, a self-report measure of physical disability may also have provided some information on the severity of physical symptoms within the MS group and the impact of this on ability to perform everyday tasks. The Expanded Disability Status Scale (EDSS; Kurtzke, 1983) is commonly used to measure physical disability and adaptive functioning in MS and would have enabled the researcher to explore the correlation between severity of physical disability and performance on the dependent variables of recall and understanding of treatment-related risk information. This may have been particularly informative given that the level of physical disability in the MS group varied from those with no real observable difficulties in mobilising to those who were dependent on carers for all tasks of daily living including personal care and meal preparation. Several studies exploring the relationship between physical disability status and cognitive impairment in MS have found a positive association between physical disability and performance on a number of neuropsychological tests including verbal memory and information processing speed (e.g. Alajbegovic et al., 2009; Lynch, Parmenter, & Denney, 2005; Patti et al., 2009). However, other studies report no significant correlation (e.g. Gaudino et al., 2001).

4.3.4. Statistical Power

The recruitment target of 60 participants was reached. This was the minimum sample size recommended in the prospective power analysis based on an expected medium

effect size of presentation condition. The actual effect size of presentation condition on recall of risk information was within the medium range ($\eta^2 = .37$). While the minimum recommended sample size was obtained, a larger sample size would have added more power to detect significant results.

The power calculation was based on a study that could be considered to be below the optimum similarity to the current study. It differed in terms of the clinical group of interest (TBI patients), levels of the presentation condition (two levels; spaced and massed), number of dependent variables (immediate recall only) and experimental paradigm (word-list learning task). Only two studies have explored the effect of spaced presentation on recall in MS (Goverover et al., 2009b; 2011). Neither of these studies were felt to be suitable for the power analysis as the effect size was small ($\eta^2 = .10$, Goverover et al., 2009b; $\eta^2 = .13$, Goverover et al., 2011), the effect size was not reported for all recall measures (only object location; Goverover et al., 2011), and one study examined the benefit of two strategies (spaced presentation and self-generation) on recall of risk information, with an emphasis on self-generation. Although using the same clinical group, both studies would also have differed from the current study in terms of the levels of presentation condition, experimental paradigm and number of dependent variables.

A number of analyses were conducted to test the four hypotheses. This may have limited the power of the study to some extent, increasing the likelihood of finding a significant result (Type 1 error).

4.3.5. Assessment Conditions

The majority of participants with MS were tested in their homes due to mobility difficulties in attending hospital. The home environment differed from a typical testing environment in terms of environmental distractions, the level of which varied across participants. This is noteworthy given that the experimental task consisted of aural extracts played on a speaker. Healthy control participants were primarily tested in their place of work. This meant that environmental distractions outside of the researchers control were also a factor in this group. Furthermore, there were more likely to be time pressures due to a participant needing to be back to work at a given time. Time of testing also varied with participants completing the test battery in the morning, afternoon or evening. Consequently, daily fluctuations in fatigue levels may also have impacted on participants' performance on measures of risk awareness.

4.3.6. Representativeness of Samples Recruited

Overall, the MS participants recruited were largely well-representative of the general MS population. The sample had a 2:1 female to male ratio (20 females, 10 males) which is slightly lower than the 2.35-3.4:1 female to male ratio universally reported in this population (Ahlgren, Oden, & Lycke, 2011; Mackenzie, Morant, Bloomfield, MacDonald, & O'Riordan, 2013; Wallin et al., 2012). The study was not powered to distinguish between performance for different MS subtypes (RRMS, PPMS, SPMS).

The mean age of the MS (49.7 years) and healthy control (45.4 years) samples were biased towards a slightly older age group. It is well-documented that some cognitive functions decline in middle age, including memory and new learning (Nilsson, 2003). It may be that the sample performed worse on measures of recall and

understanding of treatment-related risk information, although this is unlikely to have confounded group differences in risk awareness as the groups were matched for age. Nonetheless, the findings of reduced risk awareness in the MS group are likely to be less generalisable to younger MS participants. A greater benefit of spaced presentation for learning and memory has also been documented in younger relative to older adults, although both groups do benefit (Simone, Bell, & Cepeda, 2012). It is likely that an even greater benefit of spaced presentation for recall of treatment-related risk information in MS may be found in a younger MS sample. It would also be interesting to explore whether a significant benefit of spaced presentation for understanding of risk information would be found in a sample of younger MS participants.

The cognitive deficits observed in the study were largely what would be expected in an MS sample. The MS group performed significantly worse than healthy controls on a measure of information-processing speed and working memory which is in line with the evidence base detailing domain-specific MS-related cognitive impairments (Bodling et al., 2012; Denney et al., 2011; Legenfelder et al., 2003). Reduced statistical reasoning in MS has also been observed (McKnight, 2007), although this has not been widely explored. It is perhaps surprising that the MS group did not perform significantly worse than healthy controls on the CVLT-II, a measure of immediate recall. Previous studies report verbal recall memory and learning to be another common MS-related cognitive deficit (Demaree et al., 2000; Gaudino et al., 2001; Lafosse et al., 2013). However, as hypothesised, immediate recall of treatment-related risk information was significantly reduced in the MS relative to the control group. Moreover, the group difference in CVLT-II performance was significant until

Bonferroni corrections were applied. A larger sample size may have increased the power to detect a significant group difference on the CVLT-II.

4.3.7. Potentially Confounding Factor of MS Medication on Cognitive Performance

Approximately 23% of the MS group were taking prescribed DMTs. This may have been a confounding factor in that there is some recent evidence to suggest that DMTs can stabilise or improve cognitive function in MS (e.g. Iaffaldano et al., 2012; Kunkel et al., 2015). However, a significant group difference was still observed whereby the MS group performed significantly worse than healthy control participants on measures of recall and understanding of treatment-related risk information. Furthermore, a significant benefit of spaced presentation over massed presentation was still observed in the MS group for recall of risk information. Perhaps a greater benefit of spaced presentation may have been evident in a medication-naïve MS group where there may be greater compensation in light of potentially more impaired information-processing speed. Future research could explore the benefit of a spacing method of presentation of risk information when comparing two groups of MS participants, where one is prescribed DMTs and the other is a medication-naïve group.

4.4. Clinical Implications of the Study

4.4.1. Benefits of spaced presentation of treatment-related risk information in MS clinic settings

Individuals with different MS subtypes (RRMS, PPMS, SPMS) demonstrate reduced recall and understanding of treatment-related risk information relative to matched healthy controls, as well as poorer performance on measures of information-processing speed, working memory and statistical reasoning. Clinicians could use a spaced presentation method of communicating treatment-related risks and benefits to patients with MS during consultations. By interspersing this treatment information with breaks, clinicians could help to improve patients' recall of risk-benefit profiles of potential MS medications. It is likely that the benefit of spaced presentation for remembering the risks and benefits of different medication options would generalise to this clinical context where information is heard in person.

The financial cost of implementing such a strategy is minimal. However, presenting information over time and interspersed with breaks will naturally increase the amount of clinic time allocated to each MS patient in a context where clinicians' time resources are already stretched. It would be feasible for other clinical staff (for example MS nurses) to provide longer consultations in which they discuss the relative risks and benefits of various MS medication options with patients, using a spaced format, prior to them making a decision about their treatment. It would also be possible to alter the format of clinical contacts in which DMTs are discussed with patients in order to allow for timing of spaced presentation of DMT-related information. For example, some DMT-related information could be discussed,

followed by a physical exam, then further provision of DMT-related information, followed by a social and emotional review, and so on. This would provide a patient-centred approach in which the clinical contact time does not change but the format of information delivery and activities engaged in is altered to meet the needs of the patient. NICE guidelines (2003) recommend a more staged process of information provision in MS (e.g. through a number of different clinician-patient contacts). Yet, DMT information in MS clinics is currently often provided in a one-off manner rather than as a staged process likely due in large part to lack of time. Perhaps a staged process which requires a change in format of clinical contact rather than an increase in clinician time, such as that just discussed above, would be more successfully implemented. If effective, such a spaced presentation method may also help to standardise the way in which information is provided to newly diagnosed patients with MS by encouraging the uptake of a spaced or staged presentation of information in a greater number of MS clinics. However, the oral spaced presentation of information is of course just one element. Written information should also be provided (NICE, 2003) and this may further enhance recall of risk information in MS.

It has been shown that evidence-based patient information (EBPI) can lead to some improvement in risk awareness in patients with MS. Recall of treatment-related EBPI is key to the success of shared decision-making and so spaced presentation of medication risk-benefit profiles may help to make SDM a reality for patients with MS within UK health settings. Previous research has trialled the use of CDs as one means of communicating risk-benefit treatment-related information in MS (Solari et al., 2010). Presenting treatment information on a CD in a spaced format may improve the benefit of EBPI for enhancing risk awareness in MS. Not only would this reduce time

pressures for clinicians, it would also enable participants to rehearse this information at a later time when anxiety and other factors which potentially impact on risk awareness have diminished.

In a similar vein, the benefit of aural spaced presentation for recall of risk-benefit treatment information is likely to transfer to other modes of communicating spoken information such as DVDs or internet video clips. Many people with MS rely on internet-based forums to provide them with EBPI on prognosis, benefits and side-effects of treatments, advances in drug treatments, and lifestyle-relevant information (Colombo et al., 2014; Synnot et al., 2014). Links to video clips or podcasts on such websites and forums could offer another mode of presenting EBPI interspersed with breaks to patients with MS. In these clips, MS health professionals could present treatment options but could also provide educational and practical information on other topics deemed as important by patients in the aforementioned studies, such as lifestyle-relevant information. The use of spaced presentation of information may also generalise to everyday spoken conversation.

Finally, health professionals could also employ a spaced presentation strategy when assessing decision-making capacity in patients with MS. While spaced presentation does not directly improve understanding of risk information, it improves recall of complex risk information. Recall is an important component in being able to adequately understand, appreciate, and reason with risk information before expressing a well-informed choice.

4.4.2. Cognitive rehabilitation in Multiple Sclerosis

The present study adds further support to studies which suggest that altering the method of information presentation to allow more time to process information can improve cognitive function in MS. Adding in regular breaks when conveying information likely improves recall as it allows more time for the information to be encoded and processed for later retrieval from memory.

It has previously been shown that spaced presentation of information can be used to improve recall of simple information in MS such as word-lists, appointments, names, or object locations (Goverover et al., 2009b; 2011). Yet spaced presentation can also aid the recall of quite complex information. Moreover, this information does not necessarily need to be repeated in order to improve memory for information. This makes spaced presentation a potentially more realistic cognitive rehabilitation strategy to be incorporated into everyday life. It may also reduce frustration or embarrassment among patients with MS when compared with needing to ask for information to be repeated several times.

Indeed, repetition alone has not been found to reliably improve recall of risk information (Chiaravalloti et al., 2003), likely because it is not necessarily allowing extra time to process information. Chiaravalloti and colleagues (2003) showed that greater cognitive impairment in information-processing ability was associated with reduced benefit of repetition on new learning in MS. The present study suggests that new learning and immediate recall in MS can instead be optimised by presenting information in a way that increases the time available to attend to, process, and encode information, resulting in improvements in everyday functional tasks.

Cognitive impairments in information-processing speed, working memory, verbal recall, and verbal and statistical reasoning were associated with reduced recall of treatment-related risk information. Therefore, use of spaced presentation of information to improve recall in patients with MS may also have indirect benefits for these other cognitive functions. However, these remain to be explored.

4.5. Directions for Future Research

Future studies would benefit from exploring the optimal time duration of the breaks or ‘spaces’ in the spaced information-presentation condition in order to optimally enhance recall in people with MS. This optimal break time may vary as a function of cognitive load of a task. Furthermore, the benefits observed may vary based on the frequency of cognitive-deficits in the MS group. Therefore, studies exploring differences in benefit of spaced presentation on risk awareness between two MS groups, one with and one without information-processing speed deficits, would be insightful and may reveal a greater benefit of spaced presentation for recall in the MS group with information-processing speed impairments.

Future studies which recruit larger sample sizes may add further support to this benefit of spaced presentation for recall in people with MS by demonstrating a stronger effect on recall relative to massed presentation. These larger studies may also allow for the exploration of differential benefits of spaced presentation across different MS subtypes. While cognitive deficits exist across all MS subtypes, MS-related cognitive difficulties are known to worsen as the disease progresses (Benedict et al., 2006; Chiaravalloti & DeLuca, 2008). It would be interesting to see whether a greater or lesser benefit of spaced presentation for recall of risk information is evident

in later disease stages. It would also be worthwhile exploring whether spaced presentation may aid understanding of risk information in those with shorter disease duration. Perhaps cognitive deficits other than information-processing speed, for example executive dysfunction, which may impact on level of comprehension may not yet be evident in this group. Larger sample sizes would provide more power to detect a significant result in such studies.

It is important that future research continues to consider other ways of presenting information to participants with MS that might reduce the impact of slowed information-processing speed on recall of risk-information, for example, by using a teach-back method (Kripalani & Weiss, 2006) or self-generation (Goverover et al., 2011). It will be imperative for future research to also consider other more successful ways of improving understanding of risk information in MS. This may involve first identifying the cognitive abilities underlying comprehension of complex risk information. In addition, concurrent studies may develop ways of reducing the complexity of the information presented to patients in MS clinical contexts, for example by using visual aids alongside statistical information (Garcia-Retamero et al., 2012) or patient-worded information (Kusec et al., 2006). By reducing both the impact of MS-related cognitive impairments on comprehension ability as well as reducing the complexity of the information itself, participants with MS are more likely to be able to make well-informed decisions about their medical treatment in line with a true shared-decision making approach.

One other way to reduce the complexity of the treatment-related risk information presented to people with MS may be to standardise MS medication information. A consensus on how risk information should be presented would make it

easier for patients to compare across MS medications. Future studies which explore the most effective ways of presenting information about medication risks to people with MS would benefit from keeping this overarching goal in mind. Relatedly, such studies may support an argument for drug companies to simplify their style of presenting information about treatment risks. One method might be to grade the complexity of the information to be understood, for example DMTs could come with a colour coded label (e.g. red for high complexity, amber for medium complexity, and green for low complexity) indicating the complexity of the information to be processed. This would signal to patients and clinicians alike that more time may need to be allocated to the explanation and processing of red-coded DMT information.

4.6. Conclusion

The present study explored the advantages of using a spaced information-presentation style, whereby information is interspersed with breaks, to enhance risk awareness for treatment-related risk information in MS. Participants with MS performed significantly worse than healthy controls on measures of immediate recall and understanding of treatment-related risk information. Yet both groups demonstrated an equal benefit for recall from spaced presentation of information relative to continuous presentation. Reduced information-processing speed was associated with reduced recall in the MS group. Overall then, the present study provides some initial support for the advantages of using a spaced information-presentation style in order to enhance immediate recall of risk information in MS and this may be linked to MS-related deficits in information-processing speed.

Conversely, spaced presentation did not aid the comprehension of medication risk information in either the MS or healthy control groups. The breaks in information presentation may ameliorate effects of reduced information-processing speed on recall. Yet, the complexity of comprehending medication risk information may be too great a challenge for a spacing intervention to overcome in the context of MS-related cognitive impairment.

A spaced presentation strategy of presenting information about medication risks could be incorporated into MS clinical settings and may increase the potential benefits of evidence-based patient information (EBPI) in improving risk awareness in MS. Future studies would benefit from examining the optimal break time provided during spaced presentation, recruiting a larger sample size, exploring other strategies of presenting information in MS, as well as ways of reducing the complexity of the information presented. Such studies may strengthen support for the use of the spacing effect in improving recall for complex risk information and may elucidate ways of improving comprehension of risk information in MS. Ultimately then, participants with MS may be more empowered to make well-informed decisions about their medical treatment in line with a true shared-decision making approach.

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Appendices

Appendix A: Letter dated 02/04/2014 confirming NRES approval from the NRES

Committee East Midlands - Nottingham 1

Joint Research Office

Office Location:
1st Floor Maple House
149 Tottenham Court Road
London W1T 7DN

Postal Address:
UCL,
Gower Street
London WC1E 6BT

Tel: 020 3447 72177/79833 Fax: 020 3447 9937
Websites: www.uclh.nhs.uk; www.ucl.ac.uk; www.ucl.ac.uk/jro

FINAL R&D APPROVAL – NHS PERMISSION

13/05/2014

Dr Samantha Altendorff
University College London Hospitals NHS Foundation Trust
The National Hospital for Neurology and Neurosurgery
Queen Square
London
WC1N 3BG
UK

Dear Dr Samantha Altendorff,

UCLH Project ID: 14/0234 (Please quote in all correspondence)
REC Ref: 14/EM/0153
Title: The effect of spaced presentation of treatment information on recall and understanding of risk relating to medication in MS.

Thank you for registering the above study with the Joint Research Office (UCLH site). I am pleased to inform you that your study now has local R&D approval (NHS permission) to proceed and recruit participants at University College London Hospitals NHS Foundation Trust subject to sponsor confirmation.

Please note that all documents received have been reviewed and this approval is granted on the basis of the key documents provided which are ethically approved by the Research Ethics Committee:

Document	Date
REC approval and REC approved documents	02/04/2014

As Principal Investigator you are required to ensure that your study is conducted in accordance with the requirements on the attached sheet. These include the conditions of your NHS permission.

Do not hesitate to contact a member of the team should you have any queries.

Yours sincerely

P.P Professor Monty Mythen
Director of Research and Development
UCL/UCLH/Royal Free Joint Research Office

Responsibilities of the Researcher

Conditions of NHS permission

Your research has been granted NHS permission by the Joint Research Office on behalf of University College London Hospitals NHS Foundation Trust.

As a condition of the NHS permission you must comply with:

- Applicable Joint Research Office's Standard Operating Procedures
- Department of Health's Research Governance Framework for Health and Social Care
- Research Ethics Committee notice of favourable opinion
- Data Protection Act, Caldicott Principles and Trust Information Governance Policy.
- All other relevant legislation and regulatory approvals including the following *if applicable*
 - Medicines and Healthcare products Regulatory Agency
 - notice of acceptance of a clinical trial of investigational medicinal product (CTIMP)
 - notice of no objection of a clinical investigation for a medical device
 - Human Tissue Act 2004 and the Codes of Practice with special relevance to Code 9 Research
 - Human Tissue (Quality and Safety for Human Application) Regulations 2007

Responsibilities for Research Teams

As Principal Investigator you are required to ensure that:

- The roles and responsibilities of all members of the research team are documented in a delegation log and that all team members are made aware of these.
- All researchers conducting the study have applicable (up-to-date) honorary contracts.
- All researchers are suitably trained, qualified and experienced to carry out duties delegated to them and if conducting a clinical trial, have up-to-date Good Clinical Practice (GCP) training (updated every 2 years).

Responsibilities for the Principal Investigator in relation to tissue and data in the absence of a study agreement:

- After ethics approval for the study has expired, you shall ensure that tissues are disposed of in accordance with the protocol and Human Tissue Act 2004, transferred to a licensed tissue bank or used under a new ethically approved research project.
- Ensure that all necessary arrangements are in place for appropriate transfer, storage, handling, retention (archiving) and, if applicable, destruction of study data. The sponsor will act as the custodian of such data.

Reporting on Recruitment

Please ensure that you notify the Joint Research Office with:

- Confirmation of **recruiting your first patient** by emailing RandD@uclh.nhs.uk.
- There is also a requirement to report accrual on a regular basis. If your study has been adopted onto the NIHR portfolio you will be contacted directly by the NIHR Clinical Research Network Coordinating Centre. For all other studies you are required to provide an update to the Joint Research Office on recruitment every 6 months.

Reporting Study Events

Unexpected events and incidents

Please ensure that your study team reports the following **to the sponsor** as required by the protocol or sponsor SOPs:

- For **CTIMPs**
 - All suspected unexpected serious adverse events (SUSARs),
 - Protocol violations, serious breaches of protocol and of GCP
 - Urgent safety measures
- For **all other studies**
 - All unexpected serious adverse events (SAE) related to the research protocol

Please ensure that your study team reports the following **to the Joint Research Office**:

- For **all research**
 - All complaints from NHS patients from UCLH should be reported in the first instance to the UCLH NHS Complaints Manager.
 - All research related incidents occurring at the UCLH should be reported through DATIX, the Trust Incident Reporting System (available on InSight).
- For **CTIMPs**
 - Please report all SUSARs and Serious Breaches of Protocol and GCP occurring at UCLH through DATIX.
- For **all other studies**
 - Please report unexpected SAEs related to the research protocol, serious breaches of protocol and GCP if applicable through DATIX.

Study progress and changes

Please ensure that your study team reports the following to the Joint Research Office:

- Amendments (including a request to extend the study)
- Monitoring activity information:
 - for non-commercially sponsored clinical trials provide a summary of corrective and preventive actions from monitoring reports, as agreed with the sponsor
 - for industry sponsored clinical trials provide a copy of the monitoring log on an annual basis, as agreed with the sponsor
 - annual progress reports submitted to REC (for UCLH sponsored research)
- Audit activity information:
 - Notification of audits or inspections
 - Audit reports (where possible, and in agreement with the sponsor, to provide a copy of the corrective and preventive actions arising from an audit)
- Notification of end of study or suspension of study
- Publications

Study documentation

Research teams are required to:

- ◆ Prepare and maintain a site file to ensure that data and documentation associated with the study are available for audit. Please refer to the SOP for Preparation of Site File JRO/RM&G/SOP-13 available at: <http://www.ucl.ac.uk/jro/standingoperatingprocedures>
- ◆ Contact the Archivist & Records Manager by email as soon as the study has been suspended or ended in order to arrange for archiving.

If you require any further information on the above please see the Joint Research Office website <http://www.ucl.ac.uk/jro>.

Joint Research Office Standard Operating Procedures are available at:
<http://www.ucl.ac.uk/jro/standingoperatingprocedures>.

Appendix B: Letter dated 13/05/2014 confirming R and D approval from the UCLH

NHS Foundation Trust



Health Research Authority

NRES Committee East Midlands - Nottingham 1

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839697

02 April 2014

Ms Michele Burns
Trainee Clinical Psychologist
Royal Holloway, University of London
Department of Psychology
Royal Holloway, University of London
Egham, Surrey
TW20 0EX

Dear Ms Burns,

Study title:	The effect of spaced presentation of treatment information on recall and understanding of risk relating to medication in MS.
REC reference:	14/EM/0153
IRAS project ID:	144632

The Proportionate Review Sub-committee of the NRES Committee East Midlands - Nottingham 1 reviewed the above application on 02 April 2014.

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 Co-ordinator Rachel Nelson, .

Ethical opinion

There were no ethical issues.

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

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" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the 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.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

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).

Approved documents

The documents reviewed and approved were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Evidence of insurance or indemnity	Valid to 31/07/14 - Gallagher Heath	02 September 2013
Other: Appendix 1: Faux Drug Extracts in Standard Presentation Format	1	17 March 2014
Other: Appendix 2: Faux Drug Extracts in Spaced Presentation Format	1	17 March 2014
Other: Appendix 3: Record Sheets for Assessing Risk Awareness	1	17 March 2014
Other: Appendix 12: Draft GP Letter for Participant with Low Mood	1	17 March 2014
Other: Appendix 9: Invitation Letter to Companies to Participant in Research Study	1	17 March 2014
Other: Appendix 10: Advertisement for the MS Clinic Area at the National Hospital for Neurology and Neurosurgery	1	17 March 2014
Other: Appendix 11: Advertisement to Recruit Control Participants from Local Organisations	1	17 March 2014
Other: Memorandum - Research Project Approval	1	17 March 2014
Other: Investigator's CV	Michele Burns	
Other: Investigator's CV	Dawn Wendy Langdon	
Other: Bilams First Scale: Administration SDMT	Validated	
Other: CVLT-II	Validated	
Other: Confirmation of Pre-Engagement Checks (NHS to NHS Letter of Access)	1	
Participant Consent Form: Appendix 7: Informed Consent Form for MS Participants	2	01 April 2014
Participant Consent Form: Appendix 8: Informed Consent Form for Control Participants	1	17 March 2014
Participant Information Sheet: Appendix 5: Participant Information Sheet for MS Participants	2	01 April 2014
Participant Information Sheet: Appendix 6: Participant Information Sheet for Control Participants	2	01 April 2014
Protocol	1	17 March 2014
Questionnaire: Appendix 4: Measure of Understanding of Risk Information Relevant to Faux Drug Extracts	1	17 March 2014
Questionnaire: Appendix 15: Trusi-B Questionnaire		15 March 2014
Questionnaire: Fatigue Severity Scale	Validated	
Questionnaire: HAD Scale	Validated	
Questionnaire: Bicams First Scale: Patient Form SDMT	Validated	
Questionnaire: Bicams Third Scale: BVMT-R Recall	Validated	
REC application	144632/5864 39/1/52	27 March 2014

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

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.

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 NRES 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 website. Information is available at National Research Ethics Service website > After Review

14/EM/0153	Please quote this number on all correspondence
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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/>

With the Committee's best wishes for the success of this project.

Yours sincerely,



Reverend Keith Lackenby
Vice-Chair

Email: NRESCommittee.Eastmidlands-Nottingham1@nhs.net

Enclosures: List of names and professions of members who took part in the review

"After ethical review – guidance for researchers"

Copy to: Ms Annette Locke

Mr Philip Diamond

NRES Committee East Midlands - Nottingham 1

Attendance at PRS Sub-Committee of the REC meeting on 02 April 2014

Committee Members:

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Dr Ursula Holdsworth	Retired Staff Grade Community Paediatrician	Yes	
Reverend Keith Lackenby	Lay member	Yes	
Dr Ian Ross	Consultant Physician	Yes	

Also in attendance:

<i>Name</i>	<i>Position (or reason for attending)</i>
Miss Rachel Nelson	Assistant Coordinator

University College London Hospitals 
NHS Foundation Trust



National Hospital for Neurology & Neurosurgery
MS Clinic
Queen Square
London
WC1N 3BG
Website: www.uclh.nhs.uk

Department of Psychology
Doctorate in Clinical Psychology
Royal Holloway,
University of London,
Egham,
Surrey,
TW20 0EX
Email: nxjt006@live.rhul.ac.uk
Tel: 01784 414 388

Dear _____,

I would like to invite you to take part in our study investigating how well drug information is processed by people with MS and how this relates to mood and other cognitive abilities (e.g. understanding, memory, decision-making). This is an important area of research as people with MS must often choose between a number of potential drug treatments which vary in terms of their effectiveness and side effects. This study aims to inform clinicians how best to present drug treatment information in order to improve people's understanding of the different treatment options, as well as increasing confidence in their treatment decisions.

The research project is jointly co-ordinated by Dr. Samantha Altendorff (Highly Specialist Clinical Psychologist, National Hospital for Neurology and Neurosurgery) and Prof. Dawn Langdon (Clinical Psychologist, Royal Holloway University of London). We are asking people with a diagnosis of MS under the care of the National Hospital for Neurology and Neurosurgery, if they would be willing to participate. You previously indicated that you are willing to be contacted about research.

I enclose a copy of the information sheet that provides more detailed information.

Please complete the reply sheet attached to this letter and return it in the pre-paid envelope. If you are interested in participating in the research, I will contact you by telephone to provide further information and answer any questions you may have.

Thank you for considering participating in the research.
I hope to hear from you soon.

Kind Regards,

Michele Burns
Trainee Clinical Psychologist



National Hospital for Neurology & Neurosurgery
MS Clinic
Queen Square
London
WC1N 3BG
Website: www.uclh.nhs.uk

Department of Psychology
Doctorate in Clinical Psychology
Royal Holloway,
University of London,
Egham,
Surrey,
TW20 0EX
Email: nxjt006@live.rhul.ac.uk
Tel: 01784 414 388

Title of study: Risk awareness and treatment information in Multiple Sclerosis (MS)

Ethics number: 14/EM/0153

Research Participation Information Sheet:

My name is Michele Burns and I am a Trainee Clinical Psychologist. I am inviting you to take part in my research study. Before you agree to take part, it is important that you understand a bit about my reasons for undertaking this research and what it will involve. Please take some time to read the following information. Feel free to ask me for further information or to clarify anything that is unclear. Please take your time to decide whether you would like to take part. Before you decide, you may also wish to discuss this information with others, for example family or your GP.

What is the purpose of this study?

My study is exploring how well drug information is processed in patients with MS and without MS and how this relates to mood and other cognitive abilities. We have prepared some tapes with fictional drug information. These tapes will be played to you and you will also complete a number of other short tasks.

Where will this study take place?

You may choose whether you wish to undertake this study at the NHNN, at a University of London office in Central London, or at your own home. You may choose whichever is the most convenient location for you. Unfortunately no travel expenses will be available.

Why have you been asked to take part?

Most patients with MS who attend the MS clinic at the National Hospital of Neurology and Neurosurgery (NHNN) are being invited to participate.

Do you have to take part in this study?

There is no obligation for you to take part in this study. If you do decide to take part, I will ask you to sign a consent form. By signing this form you would be providing me with permission to record your contact details and to access some medical information which is of relevance to the study. Once you have provided consent, you are still free to withdraw from the study at any time without needing to provide an explanation or without any consequence to your ongoing medical care.

If you agree to participate, what will the study involve?

If you decide to take part in this study, I will ask you to attend a one-off appointment with me at a location convenient to you. This appointment will last a maximum of two hours. I will ask you to first complete a number of short questionnaires which will involve questions about your mood and level of fatigue. Then some tapes will be played on which you will hear some fictional drug information. I will also ask you to do concentration and problem solving tasks. If you feel tired, you can take breaks at any time during this appointment. If at any point you decide that you no longer want to be part of this research, you may withdraw from the study immediately without providing a reason and without any consequence to your ongoing medical care. One of the questionnaires may show that you could be depressed. In this case, you will be informed of the result and advised to see your GP.

What are the benefits to taking part?

There will be no direct benefit to you for participating in this research. However, by increasing the knowledge available on risk awareness in MS, there may be indirect benefits for future MS-related clinical practice. Additionally, my study will help you to gain more knowledge about the ways in which individuals are affected by MS. You will have the opportunity to ask questions and you will be provided with a copy of the final report once it has been published in a peer-reviewed journal. You will not be identified in any report or publication.

What are the disadvantages and risks to taking part?

Some people can find the completion of problem-solving tasks or discussions of mood or their medical conditions tiring. Please let me know if you feel tired or distressed at any point during the session. You will be free to take a break or to stop testing completely. There will also be time to talk about any concerns that you might have. Your ongoing medical care will not be affected in any way by whether you decide to take part in this study.

What will happen to the information I provide and who will have access to this?

All data will be collected and stored in accordance with the Data Protection Act 1998. Any of your personal details (e.g. name, contact details) will be kept strictly confidential and will be accessible only to myself and my supervisor Dr. Samantha Altendorff, Clinical Neuropsychologist at the NHNN. All the other information you provide will be stored anonymously and will not be linked to your personal information in any way.

This project has been approved by the NHS Research Ethics Service (NRES) and by the Research and Ethics Committee at Royal Holloway, University of London.

If you would like to ask any further questions about this research, please email me on nxjt006@live.rhul.ac.uk. You may also leave a message on 01784 414 388. Please make sure that you state clearly that your message relates to the MS research project with Michele Burns and leave your contact number. I will get back to you as soon as possible.

If you have a concern about the way in which this study is being conducted and wish to make a complaint, you may do so by contacting the study supervisor, Professor Dawn Langdon, at the following email address: D.Langdon@rhul.ac.uk

Thank you for taking the time to read this information sheet.

**Michele Burns
Trainee Clinical Psychologist and Chief Investigator**

Appendix E: Letter of invitation to partake in research study for Healthy Control

group

University College London Hospitals 
NHS Foundation Trust



National Hospital for Neurology & Neurosurgery
MS Clinic
Queen Square
London
WC1N 3BG
Website: www.uclh.nhs.uk

Department of Psychology
Doctorate in Clinical Psychology
Royal Holloway,
University of London,
Egham,
Surrey,
TW20 0EX
Email: nxjt006@live.rhul.ac.uk
Tel: 01784 414 388

Dear _____,

I would like to invite you to take part in our study investigating how well drug information is processed by people with and without Multiple Sclerosis (MS) and how this relates to mood and other cognitive abilities (e.g. understanding, memory, decision-making). This is an important area of research as people with MS must often choose between a number of potential drug treatments which vary in terms of their effectiveness and side effects. This study aims to inform clinicians how best to present drug treatment information in order to improve people's understanding of the different treatment options, as well as increasing confidence in their treatment decisions.

The research project is jointly co-ordinated by Dr. Samantha Altendorff (Highly Specialist Clinical Psychologist, National Hospital for Neurology and Neurosurgery) and Prof. Dawn Langdon (Clinical Psychologist, Royal Holloway University of London). We are asking people with and without a diagnosis of MS if they would be willing to participate. This comparison can help us to establish whether there are any important differences between healthy people and people with MS in terms of their risk awareness about treatment information.

I enclose a copy of the information sheet that provides more detailed information.

Please complete the reply sheet attached to this letter and return it in the pre-paid envelope. If you are interested in participating in the research, I will contact you by telephone to provide further information and answer any questions you may have.

Thank you for considering participating in the research.
I hope to hear from you soon.

Kind Regards,

Michele Burns
Trainee Clinical Psychologist

University College London Hospitals 
NHS Foundation Trust



National Hospital for Neurology & Neurosurgery
MS Clinic
Queen Square
London
WC1N 3BG
Website: www.uclh.nhs.uk

Department of Psychology
Doctorate in Clinical Psychology
Royal Holloway,
University of London,
Egham,
Surrey,
TW20 0EX
Email: nxjt006@live.rhul.ac.uk
Tel: 01784 414 388

Title of study: Risk awareness and treatment information in Multiple Sclerosis (MS)

Ethics number: 14/EM/0153

Research Participation Information Sheet:

My name is Michele Burns and I am a Trainee Clinical Psychologist. I am inviting you to take part in my research study. Before you agree to take part, it is important that you understand a bit about my reasons for undertaking this research and what it will involve. Please take some time to read the following information. Feel free to ask me for further information or to clarify anything that is unclear. Please take your time to decide whether you would like to take part. Before you decide, you may also wish to discuss this information with others, for example family or your GP.

What is the purpose of this study?

My study is exploring how well drug information is processed in patients with MS and without MS and how this relates to mood and other cognitive abilities. This study hopes to develop ways of helping people with MS to better understand drug information. We have prepared some tapes with fictional drug information. These tapes will be played to you and you will also complete a number of other short tasks.

What is Multiple Sclerosis (MS)?

Multiple sclerosis is a chronic neurological condition which affects the brain and spinal cord. The outside of nerve cells have become damaged and this causes a disruption in the way nerve cells communicate and transmit signals to each other. The exact cause of MS is unknown but it is likely to involve a combination of genetic and environmental factors. It is typically diagnosed in young adulthood. It is a progressive disease and so it gets worse over time. Common symptoms include fatigue, difficulty in walking and balancing, visual problems and spasms. MS is different for each individual. The severity of their symptoms will depend on the level of damage to the brain and spinal cord. There are different stages of MS. In earlier stages, many people will have periods where their symptoms subside (remission) as well as periods of varying severity in which their symptoms return (relapse). In later stages, symptoms become more permanent. There is no known cure for this condition but a number of different treatments are available including medications, diet changes, and physiotherapy.

Where will this study take place?

You may choose whether you wish to undertake this study at a University of London office in Central London, your place of work, or at another location which is convenient for you. Unfortunately no travel expenses will be available.

Why have you been asked to take part?

In order to best understand risk awareness about treatment information in MS, it is helpful to compare them to similar people from the general population who do not have MS. This comparison can help us to establish whether there are any important differences between healthy people and people with MS in terms of their risk awareness. This may also inform us about helpful ways in which we might alter the way we provide clinical services to people with MS.

Do you have to take part in this study?

There is no obligation for you to take part in this study. If you do decide to take part, I will ask you to sign a consent form. By signing this form you would be providing me with permission to record your contact details and some other personal information you might provide which is of relevance to the study. Once you have provided consent, you are still free to withdraw from the study at any time without needing to provide an explanation.

If you agree to participate, what will the study involve?

If you decide to take part in this study, I will ask you to attend a one-off appointment with me at a location convenient to you. This appointment will last for a maximum of 2 hours. I will ask you to first complete a number of short questionnaires which will involve questions about your mood and level of fatigue. I will then ask you to listen to

the fictional drug information and also to complete some concentration and problem-solving tasks. If you feel tired, you can take breaks at any time during this appointment. If at any point you decide that you no longer want to be part of this research, you may withdraw from the study immediately without providing a reason.

What are the benefits to taking part?

There will be no direct benefit to you for participating in this research. However, by increasing the knowledge available on risk awareness in MS, there may be indirect benefits for future MS-related clinical practice. Additionally, my study will help you to gain more knowledge about the ways in which individuals are affected by MS. You will have the opportunity to ask questions and you will be provided with a copy of the final report once it has been published in a peer-reviewed journal. You will not be identified in any report or publication.

What are the disadvantages and risks to taking part?

Some people can find the completion of problem-solving tasks tiring. However, it is very unusual for healthy people to feel uncomfortable. Please let me know if you feel tired or distressed at any point during the session. You will be free to take a break or to stop testing completely. There will also be time to talk about any concerns that you might have.

What will happen to the information I provide and who will have access to this?

All data will be collected and stored in accordance with the Data Protection Act 1998. Any of your personal details (e.g. name, contact details) will be kept strictly confidential and will be accessible only to myself and my supervisor Dr. Samantha Alterndorff, Clinical Neuropsychologist at the NHNN. All the other information you provide will be stored anonymously and will not be linked to your personal information in any way.

This project has been approved by the NHS Research Ethics Service (NRES) and by the Research and Ethics Committee at Royal Holloway, University of London.

If you would like to ask any further questions about this research, please email me on nxjt006@live.rhul.ac.uk. You may also leave a message on 01784 414 388. Please make sure that you state clearly that your message relates to the MS research project with Michele Burns and leave your contact number. I will get back to you as soon as possible.

If you have a concern about the way in which this study is being conducted and wish to make a complaint, you may do so by contacting the study supervisor, Professor Dawn Langdon at the following email address: D.Langdon@rhul.ac.uk

Thank you for taking the time to read this information sheet.

**Michele Burns
Trainee Clinical Psychologist and Chief Investigator**

Appendix G: Letter of request for assistance with recruitment sent to work places and organisations local to the researcher

University College London Hospitals 
NHS Foundation Trust



National Hospital for Neurology & Neurosurgery
MS Clinic
Queen Square
London
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Website: www.uclh.nhs.uk

Department of Psychology
Doctorate in Clinical Psychology
Royal Holloway,
University of London,
Egham,
Surrey,
TW20 0EX
Email: nxjt006@live.rhul.ac.uk
Tel: 01784 414 388

Dear _____,

I am writing to enquire whether you would consider allowing members of your organisation to volunteer to participate in my research study on Multiple Sclerosis (MS). The research would provide us with a greater understanding of the process of risk awareness in individuals with MS. It would help us to develop ways of improving risk awareness in individuals with MS which would in turn help them to make more balanced decisions about their medical treatment. It would also tell us how their understanding of risk relates to their mood and cognitive abilities.

In order to calibrate how well people with MS assess risk, it is necessary to investigate how well the average person performs on the same tasks. This is why I am asking for members of your organisation to participate. The study is registered as a DCLinPsy (Doctorate in Clinical Psychology) with the University of London and it is supervised by Professor Dawn Langdon, Professor of Neuropsychology at Royal Holloway, University of London, and by Dr. Samantha Altendorff, Clinical Neuropsychologist at the National Hospital for Neurology and Neurosurgery (NHNN).

Volunteers would attend an interview session involving a range of memory and concentration tasks. They would also be asked to complete a number of short questionnaires. This process would take a maximum of 2 hours to complete. The usual arrangement is for me to visit the host organisation for a day to conduct the interviews. The only personal information required from volunteers would be their age and occupation. Any data obtained from these interviews would be kept strictly confidential.

I have enclosed a participant information sheet which you may distribute to the individual volunteers. This document describes in greater detail what participation in this research study would involve. I have also enclosed a template consent form, copies of which I would bring with me. I am generally available between now and <INSERT DATE> should your organisation wish to take part. If you have any further questions, or would like to make arrangements for me to visit, I can be contacted by email (nxjt006@live.rhul.ac.uk) or at the address given at the above address. I look forward to hearing from you.

Yours sincerely,

Michele Burns
Trainee Clinical Psychologist

University College London Hospitals 
NHS Foundation Trust



National Hospital for Neurology & Neurosurgery
MS Clinic
Queen Square
London
WC1N 3BG
Website: www.uclh.nhs.uk

Department of Psychology
Doctorate in Clinical Psychology
Royal Holloway,
University of London,
Egham,
Surrey,
TW20 0EX
Email: nxjt006@live.rhul.ac.uk
Tel: 01784 414 388

Title of study: Risk awareness and treatment information in Multiple Sclerosis (MS)

Researcher: Michele Burns, Trainee Clinical Psychologist, Royal Holloway, University of London

Ethics number: 14/EM/0153

Informed Consent Form for Research Participation:

Thank you for your interest in taking part in this research. Before you agree to take part, the person organising the research must explain the project to you. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

Please tick here

- I agree that I have read the Information Sheet and understand what the study involves.
- I understand that sections of my medical notes relevant to this study may be viewed by the above named researcher. I give

my permission for this individual to access my records for the purposes of this research study.

- I understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- I understand my participation is voluntary and that if I decide at any time that I no longer wish to take part, I can notify the researchers involved and withdraw immediately without any consequence to my ongoing medical care.
- I understand that one of the questionnaires may show that I could be depressed, and if this is the case, that I will be advised to go and see my GP.
- I agree to take part in this study.

Name of Participant

Date

Signature

Name of Researcher

Date

Signature

University College London Hospitals 
NHS Foundation Trust



National Hospital for Neurology & Neurosurgery
MS Clinic
Queen Square
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Website: www.uclh.nhs.uk

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Email: nxjt006@live.rhul.ac.uk
Tel: 01784 414 388

Title of study: Risk awareness and treatment information in Multiple Sclerosis (MS)

Researcher: Michele Burns, Trainee Clinical Psychologist, Royal Holloway, University of London

Ethics number: 14/EM/0153

Informed Consent Form for Research Participation:

Thank you for your interest in taking part in this research. Before you agree to take part, the person organising the research must explain the project to you. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

Please tick here

- I agree that I have read the information sheet and understand what the study involves.
- I consent to the processing of my personal information for the purposes of this research study.

- I understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- I understand my participation is voluntary and that if I decide at any time that I no longer wish to take part, I can notify the researchers involved and withdraw immediately.
- I agree to take part in this study.

Name of Participant	Date	Signature
Name of Researcher	Date	Signature

Appendix J: Vignettes containing treatment-related risk information heard by all participants

Ganlin and Tylon Vignette

You have been diagnosed with Durkin's disease. Durkin's disease is a genetic disease. It is a chronic disease which means that there is no known cure. It is usually diagnosed in middle age when people seek their doctor's advice about difficulties with their sight. Their vision becomes increasingly restricted to a central area. If the disease is not treated, 50% of Durkin's patients would be unable to drive within five years of diagnosis. The first drug usually prescribed for Durkin's is Ganlin, which is a daily tablet. 80% of patients on Ganlin are still able to drive 10 years after diagnosis. Side effects of Ganlin are headache (30%), constipation (40%) and dry skin (20%). Some patients have more severe forms of Durkin's disease. Their eyesight continues to decline quickly even when they are taking Ganlin. These patients can be prescribed Tylon, a stronger drug. Patients given Tylon from diagnosis have a 95% chance of driving after 15 years. However, Tylon has more serious side effects. 1 in a hundred patients will suffer liver failure requiring hospitalisation in the first 10 years of use. One in a thousand will die as a result. Patients on Tylon are also three times more likely than the general population to develop dementia once they reach the age of 70.

Limac and Braddex Vignette

You have been diagnosed with Shannon's disease. It is a chronic disease which means that there is no known cure. This disease alters the shape of blood cells. This makes it more difficult for blood cells to travel through the bloodstream. This disease causes poor circulation, slow healing of wounds and bruises, and heart problems. If left untreated, 50% of patients will need heart surgery within 10 years. The usual treatment for Shannon's disease is Limac. This is a liquid medicine that needs to be taken twice a day. This medication promotes the growth of new healthy blood cells and substantially reduces the risk of further blood vessel damage. Patients on Limac have only a 1 in 100 chance of needing heart surgery after 10 years. But they often get poor circulation and excessive bruises, which can be disfiguring and rarely lead to amputations in 1 out of every 1000 patients. There is a stronger drug available for Shannon's disease called Braddex. This involves weekly injections. It has more serious side effects than Limac. Patients on Braddex hardly ever experience poor circulation or excessive bruising. However 1 in 50 will need hospitalisation for a heart attack during their lifetime, and 1 in 200 will die of a heart attack. Heart attacks can occur at any time once they start the drug.

Trixon and Fylene Vignette

You have been diagnosed with Raylick's disease. It is a chronic disease which means that there is no known cure. This is a rare disease which causes muscle wasting. Patients usually seek their doctor's advice for fatigue and difficulty walking. Sportsmen and other physically active people notice the disease earlier than the general population and are three times more likely to have Raylick's disease. There is a genetic component and once one member of a family is diagnosed, close relatives have ten times the normal risk and need to be carefully monitored. The usual treatment is Trixon, a thrice daily tablet that must be taken after food. 70% of patients who take Trixon will still be walking independently after 10 years. Sportsmen and physically active people usually have to change their lifestyle. Side effects of Trixon are sensitivity to sunlight (20%), indigestion (30%) and headache (10%). There is a stronger drug, Fylene. 99% of surviving patients on Fylene will still be walking independently after 20 years. However, Fylene has more serious side effects. One in 70 will suffer a limb fracture in the first five years and one in 200 will not recover useful limb function. In addition, one in 50 will have stomach problems requiring additional chronic medication. One in 500 on Fylene will die from stomach bleeds.

Appendix K: Scoring sheets for immediate recall of treatment-related risk information

Participant number: _____

Presented: 1st 2nd 3rd

Standard Spaced

Standard with delay

Ganlin and Tylon Vignette – Immediate Recall

You have been diagnosed with Durkin’s disease./ Durkin’s disease is a genetic disease./ It is a chronic disease which means that there is no known cure./ It is usually diagnosed in middle age/ when people seek their doctor’s advice about difficulties with their sight./ Their vision becomes increasingly restricted to a central area./ If the disease is not treated,/ 50% of Durkin’s patients/ would be unable to drive/ within five years of diagnosis./ The first drug usually prescribed for Durkin’s is Ganlin,/ which is a daily tablet./ 80% of patients on Ganlin/ are still able to drive/ 10 years after diagnosis./ Side effects of Ganlin are headache (30%),/ constipation (40%)/ and dry skin (20%)./ Some patients have more severe forms of Durkin’s disease./ Their eyesight continues to decline quickly even when they are taking Ganlin./ These patients can be prescribed Tylon,/ a stronger drug./ Patients given Tylon from diagnosis have a 95% chance/ of driving/ after 15 years./ However, Tylon has more serious side effects./ 1 in a hundred patients/ will suffer liver failure/ requiring hospitalisation/ in the first 10 years of use./ One in a thousand/ will die as a result./ Patients on Tylon are also three times more likely than the general population/ to develop dementia/ once they reach the age of 70.

Total: _____/70

Administration time: _____

Participant number: _____

Presented: 1st 2nd 3rd

Standard Spaced

Standard with delay

Limac and Braddex Vignette – Immediate Recall

You have been diagnosed with Shannon’s disease./ It is a chronic disease which means that there is no known cure./ This disease alters the shape of blood cells./ This makes it more difficult for blood cells to travel through the bloodstream./ This disease causes poor circulation,/ slow healing of wounds and bruises,/ and heart problems./ If left untreated,/ 50% of patients/ will need heart surgery/ within 10 years./ The usual treatment for Shannon’s disease is Limac./ This is a liquid medicine/ that needs to be taken twice a day./ This medication promotes the growth of new healthy blood cells/ and substantially reduces the risk of further blood vessel damage./ Patients on Limac have only a 1 in 100 chance/ of needing heart surgery/ after 10 years./ But they often get poor circulation (60%)/ and excessive bruises (40%),/ which can be disfiguring/ and rarely lead to amputations/ in 1 out of every 1000 patients./ There is a stronger drug available for Shannon’s disease/ called Braddex./ This involves weekly injections./ It has more serious side effects than Limac./ Patients on Braddex hardly ever experience poor circulation or excessive bruising./ However 1 in 50/ will need hospitalisation/ for a heart attack during their lifetime,/ and 1 in 200/ will die of a heart attack./ Heart attacks can occur at any time once they start the drug.

Total: _____/70

Administration time: _____

Participant number: _____

Presented: 1st 2nd 3rd

Standard Spaced

Standard with delay

Trixon and Fylene Vignette – Immediate Recall

You have been diagnosed with Raylick's disease./ It is a chronic disease which means that there is no known cure./ This is a rare disease which causes muscle wasting./ Patients usually seek their doctor's advice for fatigue/ and difficulty walking./ Sportsmen and other physically active people notice the disease earlier than the general population/ and are three times more likely to have Raylick's disease./ There is a genetic component/ and once one member of a family is diagnosed, close relatives have ten times the normal risk and need to be carefully monitored./ The usual treatment is Trixon,/ a thrice daily tablet/ that must be taken after food./ 70% of patients who take Trixon/ will still be walking independently/ after 10 years./ Sportsmen and physically active people usually have to change their lifestyle./ Side effects of Trixon are sensitivity to sunlight (20%),/ indigestion (30%)/ and headache (10%)./ There is a stronger drug,/ Fylene./ 99% of surviving patients on Fylene/ will still be walking independently/ after 20 years./ However, Fylene has more serious side effects./ One in 70/ will suffer a limb fracture/ in the first five years/ and one in 200/ will not recover useful limb function./ In addition, one in 50/ will have stomach problems/ requiring additional chronic medication./ One in 500/ on Fylene will die from stomach bleeds.

Total: _____/70

Administration time: _____

Appendix L: Immediate recall scoring criteria for all vignettes

Ganlin and Tylon Vignette

1. You have been diagnosed with Durkin's disease

2 points: "Durkin's disease"

1 point: N/A

2. "Durkin's disease is a genetic disease"

2 points: "genetic disease", "hereditary"

1 point: N/A

3. "It is a chronic disease which means that there is no known cure"

2 points: "chronic disease" AND "no known cure"

1 point: "chronic disease" OR "no known cure" OR indication that the illness cannot be cured

4. "It is usually diagnosed in middle age"

2 points: "diagnosed in middle age"

1 point: N/A

5. "when people seek their doctor's advice about difficulties with their sight"

2 points: "when people visit their doctor" AND "difficulties with their sight" or "vision difficulties" or "problems with eyesight"

1 point: either "when" people visit their doctor" OR "difficulties with their sight" or vision difficulties" or "problems with eyesight"

6. "Their vision becomes increasingly restricted to a central area"

2 points: "vision narrows" or "vision becomes restricted to central area"

1 point: "lose peripheral vision"

7. "If the disease is not treated"

2 points: "if untreated" "if not treated"

1 point: N/A

8. "50% of Durkin's patients"

2 points: "50%" or "half"

1 point: N/A

9. "would be unable to drive"

2 points: “no longer able to drive”

1 point: N/A

10. “within five years of a diagnosis”

2 points: “in 5 years”

1 point: N/A

11. “The first drug usually prescribed for Durkin’s is Ganlin”

2 points: “Ganlin”

1 point: N/A

12. “which is a daily tablet”

2 points: “tablet taken daily”, “tablet taken once a day”

1 point: “daily”, “once a day”, “tablet”

13. “80% of patients on Ganlin”

2 points: “80%”

1 point: N/A

14. “are still able to drive”

2 points: “can still drive”

1 point: N/A

15. “10 years after diagnosis.”

2 points: “in 10 years”

1 point: N/A

16. “Side effects of Ganlin are headache (30%)”

2 points: “headache” AND “30%”

1 point: “headache” OR “30%”

17. “constipation (40%)”

2 points: “constipation” AND “40%”

1 point: “constipation” OR “40%”

18. “and dry skin (20%)”

2 points: “dry skin” AND “20%”

1 point: “dry skin” OR “20%”

19. “Some patients have more severe forms of Durkin’s disease.”

2 points: “more severe forms”, “more serious type”

1 point: N/A

20. “Their eyesight continues to decline quickly even when they are taking Ganlin.”

2 points: “eyesight continues to get worse when taking Ganlin”

1 point: “eyesight continues to get worse”

21. “These patients can be prescribed Tylon,”

2 points: “Tylon”

1 point: N/A

22. “a stronger drug.”

2 points: “stronger drug”

1 point: “more effective drug”

23. “Patients given Tylon from diagnosis have a 95% chance”

2 points: “95% chance”

1 point: N/A

24. “of driving”

2 points: “still being able to drive”

1 point: N/A

25. “after 15 years.”

2 points: “in 15 years”

1 point: N/A

26. “However, Tylon has more serious side effects.”

2 points: “worse side effects”

1 point: N/A

27. “1 in a hundred patients”

2 points: “1 in 100”, “1%”

1 point: N/A

28. “will suffer liver failure”

2 points: “liver failure”, “liver damage”

1 point: N/A

29. “requiring hospitalisation”

2 points: “need to go to hospital”

1 point: N/A

30. “in the first 10 years of use.”

2 points: “in 10 years”

1 point: N/A

31. “One in a thousand”

2 points: “one in a thousand”

1 point: N/A

32. “will die as a result.”

2 points: “will die”, “will be fatal”

1 point: N/A

33. “Patients on Tylon are also three times more likely than the general population”

2 points: “three times greater than general population”

1 point: “three times”, “more likely than the general population”

34. “to develop dementia”

2 points: “dementia”

1 point: N/A

35. “once they reach the age of 70.”

2 points: “at 70”

1 point: N/A

Limac and Braddex Vignette

1. “You have been diagnosed with Shannon’s disease.”

2 points: “Shannon’s disease”

1 point: N/A

2. “It is a chronic disease which means that there is no known cure.”

2 points: “chronic disease with no cure”

1 point: “chronic disease”, “no cure”, “incurable”

3. “This disease alters the shape of blood cells.”

2 points: “changes shape of blood cells”

point: “affects blood cells”

4. “This makes it more difficult for blood cells to travel through the bloodstream.”

2 points: “more difficult for blood cells to travel around the body”

1 point: “impacts on blood cells”, “stops blood cells travelling”

5. “This disease causes poor circulation,”

2 points: “poor circulation”

1 point: N/A

6. “slow healing of wounds and bruises,”

2 points: “slow healing of wounds and bruises”

1 point: “slow healing of wounds”, “slow healing of bruises”

7. “and heart problems.”

2 points: “heart difficulties”, “cardio problems”

1 point: N/A

8. “If left untreated,”

2 points: “if not treated”

1 point: N/A

9. “50% of patients”

2 points: “50%”

1 point: N/A

10. “will need heart surgery”

2 points: “have heart surgery”

1 point: N/A

11. “within 10 years.”

2 points: “in 10 years”

1 point: N/A

12. “The usual treatment for Shannon’s disease is Limac.”

2 points: “Limac”

1 point: N/A

13. “This is a liquid medicine”

2 points: “liquid” AND “medicine”

1 point: “a liquid”, “a medicine”

14. “that needs to be taken twice a day.”

2 points: “twice daily”

1 point: N/A

15. “This medication promotes the growth of new healthy blood cells”

2 points: “helps new blood cells grow”

1 point: “fixes the blood cells”, “helps blood cells”

16. “and substantially reduces the risk of further blood vessel damage.”

2 points: “reduces blood cell damage”

1 point: N/A

17. “Patients on Limac have only a 1 in 100 chance”

2 points: “1 in 100”, “1%”

1 point: N/A

18. “of needing heart surgery”

2 points: “need heart operation”

1 point: “need surgery”

19. “after 10 years.”

2 points: “in 10 years”

1 point: N/A

20. “But they often get poor circulation (60%)”

2 points: “poor circulation” AND “60%”

1 point: “poor circulation” OR “60%”

21. “and excessive bruises (40%),”

2 points: “excessive bruises” AND “40%”

1 point: “excessive bruises” OR “40%”

22. “which can be disfiguring”

2 points: “disfiguring”, “unsightly”

1 point: N/A

23. “and rarely lead to amputations”

2 points: “rarely lead to amputations”

1 point: “rare side effect” OR “amputations”

24. “in 1 out of every 1000 patients.”

2 points: “1 out of 1000”

1 point: N/A

25. “There is a stronger drug available for Shannon’s disease”

2 points: “stronger drug”

1 point: “more effective drug”

26. “called Braddex.”

2 points: “Braddex”

1 point: N/A

27. “This involves weekly injections.”

2 points: “weekly” AND “injections”

1 point: “weekly”, “once a week” OR “injections”, “needle”

28. “It has more serious side effects than Limac.”

2 points: “worse side effects”

1 point: N/A

29. “Patients on Braddex hardly ever experience poor circulation or excessive bruising.”

2 points: “poor circulation or excessive bruising is rare”

1 point: “no poor circulation” “no bruising”

30. “However 1 in 50”

2 points: “1 in 50”, “2%”

1 point: N/A

31. “will need hospitalisation”

2 points: “need to go to hospital”

1 point: N/A

32. “for a heart attack during their lifetime,”

2 points: “for a heart attack at some time in their life”

1 point: “for a heart attack” OR “at some time in their life”

33. “and 1 in 200”

2 points: “1 in 200”

1 point: N/A

34. “will die of a heart attack.”

2 points: “will die from heart attack”

1 point: “will die

35. “Heart attacks can occur at any time once they start the drug.”

2 points: “at any time”

1 point: N/A

Trixon and Fylene Vignette

1. “You have been diagnosed with Raylick’s disease.”

2 points: “Raylick’s disease”

1 point: N/A

2. “It is a chronic disease which means that there is no known cure.”

2 points: “chronic disease with no cure”

1 point: “chronic disease”, “no cure”, “incurable”

3. “This is a rare disease which causes muscle wasting.”

2 points: “rare muscle wasting disease”

1 point: “rare disease” OR “muscle wasting disease”

4. “Patients usually seek their doctor’s advice for fatigue”

2 points: “go to doctor about fatigue”

1 point: “go to doctor”, “fatigue”, “tiredness”

5. “and difficulty walking.”

2 points: “trouble walking”

1 point: “mobility difficulties”

6. “Sportsmen and other physically active people notice the disease earlier than the general population”

2 points: “Sportsmen and active people spot it earlier than most people”

1 point: “Sportsmen notice it earlier”, “Active people notice it earlier”,
“Sportsmen and active people get it”

7. “and are three times more likely to have Raylick’s disease.”

2 points: “three times”, “30%”

1 point: N/A

8. “There is a genetic component”

2 points: “it’s genetic”. “hereditary”

1 point: N/A

9. “and once one member of a family is diagnosed, close relatives have ten times the normal risk and need to be carefully monitored.”

2 points: “relatives are ten times more likely to get it and need to watch carefully”
1 point: “relatives are ten times more likely to get it” OR “relatives must watch carefully”

10. “The usual treatment is Trixon,”

2 points: Trixon
1 point: N/A

11. “a thrice daily tablet”

2 points: “tablet taken three times a day”
1 point: “tablet” OR “three times a day”

12. “that must be taken after food.”

2 points: “take after food”
1 point: N/A

13. “70% of patients who take Trixon”

2 points: “70%”
1 point: N/A

14. “will still be walking independently”

2 points: “will still be walking”
1 point: N/A

15. “after 10 years.”

2 points: “in 10 years”
1 point: N/A

16. “Sportsmen and physically active people usually have to change their lifestyle.”

2 points: “
1 point:

17. “Side effects of Trixon are sensitivity to sunlight (20%),”

2 points: “sensitivity to sunlight” AND “20%”
1 point: “sensitivity to sunlight” OR “20%”

18. “indigestion (30%)”

2 points: “indigestion” AND “30%”
1 point: “indigestion” OR “30%”

19. “and headache (10%).”

2 points: “headache” AND “10%”

1 point: “headache” OR “10%”

20. “There is a stronger drug,”

2 points: “stronger drug”

1 point: “more effective drug”

21. “Fylene.”

2 points: “Fylene”

1 point: N/A

22. “99% of surviving patients on Fylene”

2 points: “99%”

1 point: N/A

23. “will still be walking independently”

2 points: “will still be walking”

1 point: N/A

24. “after 20 years.”

2 points: “in 20 years”

1 point: N/A

25. “However, Fylene has more serious side effects.”

2 points: “worse side effects”

1 point: N/A

26. “One in 70”

2 points: “1 in 70”

1 point: N/A

27. “will suffer a limb fracture”

2 points: “limb fracture”, “break a limb”

1 point: “break a bone”

28. “in the first five years”

2 points: “in 5 years”

1 point: N/A

29. “and one in 200”

2 points: “one in 200”

1 point: N/A

30. “will not recover useful limb function.”

2 points: “will not regain use of the limb”

1 point: “will not recover”

31. “In addition, one in 50”

2 points: “one in 50”, “2%”

1 point: N/A

32. “will have stomach problems”

2 points: “stomach difficulties”

1 point: N/A

33. “requiring additional chronic medication.”

2 points: “requiring more medication”

1 point: N/A

34. “One in 500”

2 points: “One in 500”

1 point: N/A

35. “on Fylene will die from stomach bleeds.”

2 points: “will die from stomach bleeds”, “will suffer fatal stomach bleeds”

1 point: “will die”, “will have stomach bleeds”

Appendix M: Measures of understanding of treatment-related risk information

Measure of understanding of risk information relevant to Ganlin and Tylon Vignette:

- Q. 1. What is the chance that you will suffer from headaches after taking Ganlin?
- Q. 2. How likely is it that you will experience symptoms such as dry skin after taking Ganlin?
- Q. 3. What are the first signs of Durkin's Disease?
- Q. 4. Who is more likely to develop Durkin's Disease?
- Q. 5. How effective is Ganlin in terms of the percentage of people able to drive following diagnosis?
- Q. 6. How long can you expect to drive if Durkin's Disease is left untreated?
- Q.7. How common is liver failure in someone who is taking Tylon?
- Q.8. How much more likely is someone to develop dementia when prescribed Tylon?

Measure of understanding of risk information relevant to Limac and Braddex Vignette:

- Q. 1. What is the chance that you will need to undergo limb amputation after taking Limac?
- Q. 2. How typical is it for someone with untreated Shannon's disease to require heart surgery?
- Q. 3. How likely is it that you will suffer from poor circulation while taking Limac?
- Q. 4. How likely is it that you will suffer from excessive bruising while taking Limac?
- Q. 5. What are the first symptoms of Shannon's Disease?
- Q. 6. How effective is Limac in terms of the number of people requiring heart surgery when prescribed this medication?
- Q.7. How common is hospitalisation for heart attacks in those who are prescribed Braddex?
- Q.8. What is the risk of death for individuals who are prescribed Braddex?

Measure of understanding of risk information relevant to Trixon and Fylene Vignette:

- Q. 1. What is the chance that you will suffer headaches after taking Trixon?
- Q. 2. What is the chance that you will suffer sensitivity to sunlight after taking Trixon?
- Q. 3. What are the initial symptoms you might experience with Raylick's Disease?
- Q. 4. How effective is Trixon in terms of the number of people able to walk independently 10 years after diagnosis?
- Q. 5. What is the risk of death in those who are prescribed Fylene?
- Q. 6. There is an increased risk of developing Raylick's Disease in relatives of those with a diagnosis; how big is this increased risk?
- Q. 7. How effective is Fylene in terms of the number of people who maintain the ability to walk independently 20 years after diagnosis?
- Q. 8. How common is limb fracture in those who are prescribed Fylene?

Appendix N: Measures of understanding of treatment-related risk information scoring criteria for all vignettes

Ganlin and Tylon Vignette

Q. 1. What is the chance that you will suffer from headaches after taking Ganlin?

2 points: 30% OR 3 in 10 OR 30 in 100

1 point: N/A

Q. 2. How likely is it that you will experience symptoms such as dry skin after taking Ganlin?

2 points: 20% OR 2 in 10 OR 20 in 100

1 point: N/A

Q. 3. What are the first signs of Durkin's Disease?

2 points: "Difficulties with sight/vision" OR "vision becomes restricted to a central area" OR "loss of peripheral vision"

1 point: N/A

Q. 4. Who is more likely to develop Durkin's Disease?

2 points: "people in middle-age"

1 point: N/A

Q. 5. How effective is Ganlin in terms of the percentage of people able to drive following diagnosis?

2 points: 80% or 8 in 10 people or 80 in 100 people

1 point: N/A

Q. 6. How long can you expect to drive if Durkin's Disease is left untreated?

2 points: 5 years

1 point: N/A

Q.7. How common is liver failure in someone who is taking Tylon?

2 points: 1 in 100 patients OR 1%

1 point: N/A

Q.8. How much more likely is someone to develop dementia when prescribed Tylon?

2 points: 3 times

1 point: N/A

Limac and Braddex Vignette

Q. 1. What is the chance that you will need to undergo limb amputation after taking Limac?

2 points: 1 in 1000 patients

1 point: N/A

Q. 2. How typical is it for someone with untreated Shannon's disease to require heart surgery?

2 points: 50% OR 5 in 10 OR 50 in 100 OR "half"

1 point: N/A

Q. 3. How likely is it that you will suffer from poor circulation while taking Limac?

2 points: 60% OR 6 in 10 chance OR 60 in 100

1 point: N/A

Q. 4. How likely is it that you will suffer from excessive bruising while taking Limac?

2 points: 40% OR 4 in 10 OR 40 in 100

1 point: N/A

Q. 5. What are the first symptoms of Shannon's Disease?

2 points: 2 of 3 of the following: "poor circulation", "slow healing of wounds and/or bruises", "heart problems"

1 point: 1 of the following: "poor circulation", "slow healing of wounds and/or bruises", "heart problems"

Q. 6. How effective is Limac in terms of the number of people requiring heart surgery when prescribed this medication?

2 points: 1 in 100 chance OR 1%

1 point: N/A

Q.7. How common is hospitalisation for heart attacks in those who are prescribed Braddex?

2 points: 1 in 50 OR 2%

1 point: N/A

Q.8. What is the risk of death for individuals who are prescribed Braddex?

2 points: 1 in 200

1 point: N/A

Trixon and Fylene Vignette

Q. 1. What is the chance that you will suffer headaches after taking Trixon?

2 points: 10% OR 1 in 10 OR 10 in 100

1 point: N/A

Q. 2. What is the chance that you will suffer sensitivity to sunlight after taking Trixon?

2 points: 20% OR 2 in 10 OR 20 in 100

1 point: N/A

Q. 3. What are the initial symptoms you might experience with Raylick's Disease?

2 points: Must say "fatigue" AND "difficulty walking/reduced mobility"

1 point: Either "fatigue" OR "difficulty walking/reduced mobility"

Q. 4. How effective is Trixon in terms of the number of people able to walk independently 10 years after diagnosis?

2 points: 70% OR 7 in 10 OR 70 in 100

1 point: N/A

Q. 5. What is the risk of death in those who are prescribed Fylene?

2 points: 1 in 500

1 point: N/A

Q. 6. There is an increased risk of developing Raylick's Disease in relatives of those with a diagnosis; how big is this increased risk?

2 points: 10 times OR 10 fold

1 point: N/A

Q. 7. How effective is Fylene in terms of the number of people who maintain the ability to walk independently 20 years after diagnosis?

2 points: 99% OR 99 in 100

1 point: N/A

Q. 8. How common is limb fracture in those who are prescribed Fylene?

2 points: 1 in 70

1 point: N/A

Appendix O: California Verbal Learning Test (CVLT-II) score sheet

This material is unavailable due to copyright restrictions.

Appendix P: Symbol Digit Modalities Test (SDMT) score sheet

This material is unavailable due to copyright restrictions.

Appendix Q: Verbal and Spatial Reasoning Test (VESPAR) score sheet

This material for both the Verbal Analogies and Verbal Series subtests is unavailable due to copyright restrictions.

Appendix R: Arithmetic subtest of the Wechsler Adult Intelligence Scale-Third
Edition (WAIS-III) Scoring Sheet

This material is unavailable due to copyright restrictions.

TRUSI

On the following pages is a series of questions involving numbers. Please read each question and answer by circling **one** of the options given below the question.

These questions are not taken from the real world. They are designed purely for this questionnaire to work out how good people are at dealing with numbers.

If you do not know what the answer is, please take your **best guess**.

If you change your mind, **clearly cross out your first answer and circle another option**

Example:

A quarter of all men are at least 6 feet tall.

What are the chances that any man you meet is at least 6 feet tall?

- | | | | |
|---------------|------|----|------|
| A. | 6 % | E. | 45 % |
| B. | 15 % | F. | 50 % |
| C. | 25 % | G. | 65 % |
| D. | 35 % | H. | 75 % |

There will be three sets of questions:

- 1) Questions about everyday things.
- 2) Questions about health risks.
- 3) Questions about health risks to do with Multiple Sclerosis (MS).

These questions are not designed to catch you out. However, they are not all easy and very few people will get them all right.

Over the page are some practice questions:

Please circle **only one** of the available options

One in every two UK citizens goes on holiday in Britain each year?

What are the chances that any UK citizen you meet goes on holiday in Britain each year?

- | | |
|---------------|----------------|
| A. 1% | E. 20% |
| B. 2% | F. 50% |
| C. 5% | G. 80% |
| D. 10% | H. 100% |

Lupus is a potentially fatal medical condition. 20% of people with Lupus will need a prolonged hospital stay.

So far this year, 100 people have been diagnosed with Lupus in the UK. How many of them will require a prolonged hospital stay?

- | | |
|--------------|---------------|
| A. 1 | E. 20 |
| B. 2 | F. 50 |
| C. 5 | G. 80 |
| D. 10 | H. 100 |

There are twice as many diagnoses of Secondary Progressive MS each year as there are diagnoses of Primary Progressive MS.

If there were 45 diagnoses of Primary Progressive MS last year, how many diagnoses of Secondary Progressive MS were there?

- | | |
|--------------|---------------|
| A. 2 | E. 135 |
| B. 22 | F. 180 |
| C. 45 | G. 360 |
| D. 90 | H. 450 |

These questions are about everyday things.

Please circle **only one** of the available options

In the UK, 34% of people say apples are their favourite fruit, 38% say that bananas are their favourite fruit and 28% say some other fruit is their favourite.

What are the chances that someone buying their favourite fruit in a shop will not be buying apples?

- | | |
|--------|--------|
| A. 4% | E. 34% |
| B. 6% | F. 38% |
| C. 10% | G. 66% |
| D. 28% | H. 72% |

There are ten used vehicles parked on the forecourt of an approved car dealership. Eight of them are 2006 registered, one is 2005 registered and one is 2003 registered.

If one vehicle is sold that morning, what are the chances that it is 2006 registered?

- | | |
|--------|---------|
| A. 10% | E. 60% |
| B. 15% | F. 80% |
| C. 20% | G. 95% |
| D. 50% | H. 100% |

Oldport council have surveyed their residents to find out whether their refuse bins are big enough. 25% of people said that their rubbish didn't fit in their bins less than once a month. 39% said that their rubbish always fitted into their bin.

Of 200 people living in Walmsley Road in Oldport how many said that their rubbish always fitted into their bins?

- | | |
|-------|--------|
| A. 9 | E. 78 |
| B. 25 | F. 98 |
| C. 39 | G. 112 |
| D. 50 | H. 131 |

Tiny animals called “grewcocks” can attach themselves to the wings of domestic swallows to keep warm. 2 out of 10 domestic swallows with “grewcocks” attached will not be able to fly because of this.

If there are 15 swallows with “grewcocks” attached to their wings, how many will not be able to fly because of this?

- | | |
|------|-------|
| A. 2 | E. 6 |
| B. 3 | F. 8 |
| C. 4 | G. 9 |
| D. 5 | H. 15 |

Many British people travel to New York for a holiday. 2 out of 3 of those people will be able to use their mobile phones to call home.

In a hotel lobby in New York, how likely is it that a British tourist sitting next to you will be able to call home on their mobile phone?

- | | |
|--------|--------|
| A. 22% | E. 50% |
| B. 33% | F. 54% |
| C. 40% | G. 60% |
| D. 45% | H. 67% |

In a new type of sweet called Tongue-Flamers, 20% are red, 20% are green, 20% are blue and 40% are yellow.

If you pick one without looking, what are the chances it is blue?

- | | |
|------------|-------------|
| A. 1 in 2 | E. 1 in 40 |
| B. 1 in 4 | F. 1 in 50 |
| C. 1 in 5 | G. 1 in 80 |
| D. 1 in 20 | H. 1 in 100 |

According to Government Statistics, working-age mothers are less likely to be in employment than working-age women without children. In fact 68% of working-age mothers are employed compared with 73% of working-age women without children.

In a typical group of 200 working-age women, of whom 100 have children, how many will be employed?

- | | |
|--------|--------|
| A. 5 | E. 141 |
| B. 68 | F. 150 |
| C. 73 | G. 168 |
| D. 111 | H. 173 |

15% of Horse Chestnut trees are infected with a disease called Firkins Canker. Around 2 out of 10 infected trees will die within 10 years.

What are the chances that any Horse Chestnut tree will die from Firkins Canker in the next 10 years?

- | | |
|--------|--------|
| A. 3% | E. 17% |
| B. 5% | F. 20% |
| C. 8% | G. 25% |
| D. 15% | H. 30% |

50% of graduates leave University without a job. An ambitious graduate employment agency plans to reduce the amount of graduates leaving University without a job by 20%

What proportion of graduates will leave University without a job if the agency is successful?

- | | |
|--------|--------|
| A. 10% | E. 50% |
| B. 20% | F. 55% |
| C. 30% | G. 60% |
| D. 40% | H. 70% |

8 times out of 10, the leading brand of biological washing powder will completely remove cooking-oil stains. If the oil stain is left overnight, however, the washing powder will only be 1/3 as effective.

If you are about to wash 15 oil-stained chef outfits from last night's Superchef 2008 competition, how many will be completely clean after washing with the leading brand of powder?

- | | | | |
|----|---|----|----|
| A. | 2 | E. | 10 |
| B. | 3 | F. | 11 |
| C. | 4 | G. | 12 |
| D. | 5 | H. | 15 |

The UK Tourist Regulatory Committee reported that:

On the upcoming August Bank Holiday, we predict there will be an 18% chance of experiencing minor delays in reaching holiday destinations.

Which of the following is the best interpretation of this information?

- A. If you go on holiday at this time, plan a little extra time for potential delays.
- B. People's travel times are likely to be 18% longer than timetabled.
- C. Travel to 18% of holiday destinations will be delayed.
- D. There's not too much chance of delay if you plan carefully.
- E. 18 out of 100 holiday journeys will be slightly delayed in reaching their destinations.
- F. Other (Please explain below)

.....
.....

These questions are about health risks.

Please circle **only one** of the available options

Your GP tells you that there is something unusual about a recent blood test. The GP says that in around 65% of similar cases, a rest would cure the problem. However, in 26% there is something that will need very urgent treatment and in the remaining 9% further investigation will be necessary.

What are the chances that you will need more than a rest?

- | | |
|--------|---------|
| A. 9% | E. 50% |
| B. 26% | F. 74% |
| C. 35% | G. 91% |
| D. 39% | H. 100% |

Of 1000 serious Road Traffic Accidents included in a study of accidents in the UK, 800 involved a motorbike, 100 involved a car, and 100 involved a heavy goods vehicle.

If this survey is a fair reflection the UK as a whole what are the chances that any serious Road Traffic Accident involved a heavy goods vehicle?

- | | |
|--------|---------|
| A. 10% | E. 60% |
| B. 15% | F. 80% |
| C. 20% | G. 95% |
| D. 50% | H. 100% |

Deep Vein Thrombosis (DVT) is a very serious medical condition which is common in people who travel long distances by plane. However, the risk can be reduced by taking aspirin before travelling. 17% of people said that they take aspirin before travelling by plane, while 79% of people said that they did not take aspirin before flying.

If you ask 200 people in an airport about what they take before flying, how many will say that they do not take aspirin?

- | | |
|-------|--------|
| A. 17 | E. 96 |
| B. 34 | F. 100 |
| C. 52 | G. 117 |
| D. 79 | H. 158 |

MRSA and CDiff are two sorts of resistant “superbug” which can have severe effects on people who are ill in hospital, including death. 15 out of 25 people admitted to Hospital come into contact with one of these “superbugs”.

If 60 people are admitted to an inpatient ward next month, how many of them will come into contact with MRSA or CDiff?

- | | |
|-------|-------|
| A. 10 | E. 30 |
| B. 15 | F. 36 |
| C. 18 | G. 40 |
| D. 28 | H. 60 |

There is concern about industrial mercury in the environment. Extensive damage to those industries’ safety systems could result in widespread mercury contamination. 2 out of 5 people with mercury contamination will experience memory problems.

If you find out too late that your water supply has been contaminated with mercury, what are the chances of experiencing memory problems as a result of the contamination?

- | | |
|--------|--------|
| A. 3% | E. 20% |
| B. 5% | F. 36% |
| C. 8% | G. 40% |
| D. 10% | H. 60% |

The Agency for Health Improvement (AHI) reported in 1999 that the most common causes of death in UK adults are: Cancer 15%, Myocardial Infarction (Heart Attack) 61%, Other Causes 14%.

What are the chances that any adult will die of cancer?

- | | |
|-------------|------------|
| A. 1 in 100 | E. 4 in 15 |
| B. 1 in 15 | F. 4 in 10 |
| C. 3 in 20 | G. 3 in 5 |
| D. 2 in 10 | H. 9 in 10 |

The Greater London Incident Prevention Research Council (GL-IPRC) reported last year that households *without* approved electrical circuitry were more likely than those *with* such circuitry to report a fatal household accident. Whereas 4.9% of households without approved circuitry reported a fatal accident, only 3.1% of approved households made such a report.

In 200 typical Greater London households, where half of them have approved circuitry, how many fatal accidents were reported last year?

- | | | | |
|----|----|----|----|
| A. | 1 | E. | 31 |
| B. | 8 | F. | 49 |
| C. | 15 | G. | 67 |
| D. | 18 | H. | 80 |

It is estimated that there is a 10% chance of the H5N1 “Bird Flu” virus mutating to infect humans who have contact with infected birds. The results are likely to be fatal in 6 out of 20 human cases.

What are the chances that human contact with an infected bird will result in human death?

- | | | | |
|----|------|----|-----|
| A. | 1.5% | E. | 15% |
| B. | 3% | F. | 20% |
| C. | 10% | G. | 25% |
| D. | 13% | H. | 30% |

Only 40% of people diagnosed with asbestosis will survive more than ten years from time of diagnosis. If they do not begin treatment within two months of diagnosis, this survival rate drops by 30%.

If you have been diagnosed with asbestosis four months ago and have not begun treatment, what are your chances of surviving beyond the next ten years?

- | | | | |
|----|-----|----|-----|
| A. | 5% | E. | 28% |
| B. | 10% | F. | 30% |
| C. | 14% | G. | 40% |
| D. | 16% | H. | 68% |

Over a 20 year period, Accident and Emergency services in rural Eastern England report that 1 in 4 working-age adults who are struck by lightning will die as a result. If the person under 40, however, the strike will only be 1/3 as lethal.

If 12 people under 40 were struck by lightning between 1987 and 2006, how many died?

- | | | | |
|----|---|----|----|
| A. | 1 | E. | 8 |
| B. | 3 | F. | 10 |
| C. | 4 | G. | 11 |
| D. | 7 | H. | 12 |

In the news it says: In London, a recent survey has found that there is now a 17% chance of being a victim of street crime.

Which of the following is the best interpretation of this information?

- A. If you live in London, there's a good chance you'll be the victim of street crime.
- B. Street crime occurs in 17% of the London area.
- C. You will be mugged 17% of the time you're out.
- D. 17 out of every 100 people in London will be the victim of street crime.
- E. If you live in London, you're pretty unlikely to be a victim street crime.
- F. Other (Please explain below)

.....

.....

These questions are about health risks to do with MS.

Please circle **only one** of the available options

In the UK, 64% of Relapsing-Remitting MS patients say their worst fear is becoming wheelchair-bound, 27% say that it is loss of mental abilities and 9% said they most feared becoming hopeless.

What are the chances that someone with Relapsing-Remitting MS has a worst fear which is not about their physical mobility?

- | | |
|--------|--------|
| A. 9% | E. 55% |
| B. 18% | F. 64% |
| C. 27% | G. 73% |
| D. 36% | H. 91% |

Five people with a diagnosis of Multiple Sclerosis are in the waiting area at a West London MS clinic. Three of them have a diagnosis of Relapsing-Remitting MS, one has benign MS and one has Secondary Progressive MS.

What are the chances that first person called in has Secondary Progressive MS?

- | | |
|--------|--------|
| A. 1% | E. 20% |
| B. 3% | F. 40% |
| C. 5% | G. 50% |
| D. 10% | H. 80% |

In the United Kingdom, there have been some rare reports of unrelated health issues being wrongly diagnosed as Multiple Sclerosis. 80% of people who turned out to have been wrongly diagnosed had sought only one previous medical opinion. 15% of people who turned out to have been wrongly diagnosed had sought two previous medical opinions.

In 200 people who have been wrongly diagnosed, how many had sought two previous medical opinions?

- | | |
|-------|--------|
| A. 15 | E. 95 |
| B. 30 | F. 160 |
| C. 40 | G. 170 |
| D. 80 | H. 185 |

It is common for people with MS to experience debilitating fatigue. 6 in every 10 people with Secondary Progressive MS will be too fatigued to leave the house more than twice a week.

If there are 25 people with Secondary Progressive MS, how many of them will be too fatigued to leave the house more than twice a week?

- | | |
|------|-------|
| A. 1 | E. 10 |
| B. 4 | F. 12 |
| C. 6 | G. 15 |
| D. 8 | H. 25 |

A at any given time, some people with Relapsing-Remitting MS are experiencing a relapse. Intensive community support will be required by 3 out of 5 people with Relapsing-Remitting MS during relapse.

If you have Relapsing-Remitting MS and are currently experiencing a relapse, what are the chances that you will need intensive community support?

- | | |
|--------|--------|
| A. 1% | E. 50% |
| B. 3% | F. 60% |
| C. 10% | G. 70% |
| D. 20% | H. 90% |

In an East London community disability service, an Admin Assistant explored Physiotherapy waiting list times for people with MS. 20% of people with MS had to wait less than a month, 18% had to wait between one and three months, 25% had to wait between three and six months and 15% were never seen.

If you have been referred for Physiotherapy to this service, what are the chances you will have to wait between three and six months?

- | | |
|------------|------------------|
| A. 1 in 2 | E. 3 in 10 |
| B. 1 in 4 | F. 3 in 18 |
| C. 1 in 5 | G. 1 in 25 |
| D. 3 in 20 | H. $\frac{3}{4}$ |

A regional survey of people with MS found that significantly more people over 35 had experienced a progressive worsening of their condition in the last five years than those under 35. In fact, 10% of under 35's said that they had experienced progressive worsening compared with 48% of people over 35.

If 200 people were surveyed, of whom 100 were under 35 how many people had experienced a progressive worsening in the last five years?

- | | |
|-------|--------|
| A. 10 | E. 53 |
| B. 20 | F. 58 |
| C. 29 | G. 96 |
| D. 48 | H. 100 |

Tozaril, a new drug for the prevention of relapse in Relapsing-Remitting MS has been distributed to 25% of UK Pharmacies. Despite the high demand for Tozaril, only 4 out of 10 of these Pharmacies have decided to sell it during the first six months.

If you have a prescription for the drug, what are the chances that any pharmacist you go to in the next six months will sell you the drug?

- | | |
|--------|--------|
| A. 4% | E. 25% |
| B. 6% | F. 35% |
| C. 10% | G. 40% |
| D. 15% | H. 50% |

A herbal remedy, Calmadol, is reported to reduce urinary infections in people with Relapsing-Remitting MS by 5%.

If in the last year you have had urinary infections roughly 20% of the time, how much of next year would you expect to have a urinary infection if you start taking Calmadol?

- | | |
|--------|--------|
| A. 1% | E. 19% |
| B. 5% | F. 20% |
| C. 6% | G. 25% |
| D. 15% | H. 50% |

9 times out of 10, a clinic that sees people with suspected neurological problems can correctly diagnose MS. However, if the clinic does not have use of a Stelleron MRI scanner, the diagnosis is only 2/3 as reliable.

If your GP sends you to a clinic that does not have use of a Stelleron MRI scanner and the clinic says that you have MS, what are the chances the diagnosis is correct?

- | | |
|--------|--------|
| A. 9% | E. 40% |
| B. 10% | F. 60% |
| C. 19% | G. 67% |
| D. 25% | H. 90% |

On the side of a bottle of prescription medication for prevention of relapses, it says:

If taken alongside antibiotics there is a 10% chance of developing a kidney problem. If you notice any pain passing water, consult your physician.

Which of the following is the best interpretation of this warning?

- A. Don't use the medication if you're on antibiotics, there's a good chance of developing a kidney problem.
- B. If you're on antibiotics, take only 10% of the recommended dose.
- C. If you develop a kidney problem, it will probably affect 10% of the kidney tissue.
- D. About 10 out of 100 people on antibiotics who use this medication will develop a kidney problem.
- E. If you are on antibiotics, there is hardly any chance of developing a kidney problem.
- F. Other (Please explain below)

.....

.....

Thank you very much for completing this Questionnaire.

As explained at the beginning, none of the facts in the questions were true. They are imaginary examples to help us understand how good people are at dealing with numbers relating to the world and to situations affecting their health.

Appendix T: Wechsler Test of Adult Reading (WTAR) Scoring Sheet

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Appendix U: Modified Token Test (MTT)

Modified Token Test

Using Weigl's Blocks in Random Array

1. Put the red circle on the green triangle.
2. Put the blue square behind the yellow circle.
3. Touch the blue circle with the red triangle.
4. Pick up the blue circle OR the red triangle.
5. Put the green square away from the yellow square.
6. If there is a black circle, pick up the red triangle. (Note. There is no black circle).
7. When I touch the green circle, you take the green square. (Note. Wait a few seconds before touching the green circle).
8. Put the green square beside the red circle.
9. Touch the squares, slowly and the circles, quickly.
10. Put the red circle between the yellow triangle and the green triangle.
11. Except for the green one, touch the circles.
12. Instead of the blue square, take the yellow circle.
13. Together with the yellow circle, take the blue circle.
14. After picking up the green square, touch the red circle.
15. Before touching the yellow circle, pick up the red square.

Scoring notes

Item No. 2: 'Behind' may be interpreted either with respect to the patient or the examiner (if facing the patient). Thus it may be necessary to ascertain which interpretation the patient has adopted. Credit is also given if the blue square is put under the yellow circle. Item No. 9: Omission of one circle and/or one square is permitted.

Appendix V: Hospital Anxiety and Depression Scale (HADS) score sheet

Hospital Anxiety and Depression Scale (HADS)

This questionnaire is designed to help the researcher to know how you feel. Read each item below and place a **tick** in the box opposite the reply which comes closest to how you have been feeling in **the past week**. Tick only one box in each section.

Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long, thought-out response.

I feel tense or 'wound up'

- | | |
|---------------------------------|--------------------------|
| Most of the time | <input type="checkbox"/> |
| A lot of the time | <input type="checkbox"/> |
| From time to time, occasionally | <input type="checkbox"/> |
| Not at all | <input type="checkbox"/> |

I still enjoy the things I used to enjoy

- | | |
|--------------------|--------------------------|
| Definitely as much | <input type="checkbox"/> |
| Not quite so much | <input type="checkbox"/> |
| Only a little | <input type="checkbox"/> |
| Hardly at all | <input type="checkbox"/> |

I get a sort of frightened feeling as if something awful is about to happen

- | | |
|------------------------------------|--------------------------|
| Very definitely and quite badly | <input type="checkbox"/> |
| Yes, but not too badly | <input type="checkbox"/> |
| A little, but it does not worry me | <input type="checkbox"/> |
| Not at all | <input type="checkbox"/> |

I can laugh and see the funny side of things

- | | |
|----------------------------|--------------------------|
| As much as I always could | <input type="checkbox"/> |
| Not quite so much now | <input type="checkbox"/> |
| Definitely not so much now | <input type="checkbox"/> |
| Not at all | <input type="checkbox"/> |

Worrying thoughts go through my mind

- | | |
|--------------------------|--------------------------|
| A great deal of the time | <input type="checkbox"/> |
| A lot of the time | <input type="checkbox"/> |
| Not too often | <input type="checkbox"/> |
| Very little | <input type="checkbox"/> |

I feel cheerful

- Never
- Not often
- Sometimes
- Most of the time

I can sit at ease and feel relaxed

- Definitely
- Usually
- Not often
- Not at all

I feel as if I am slowed down

- Nearly all the time
- Very often
- Sometimes
- Not at all

**I get a sort of frightened feeling like
'butterflies' in the stomach**

- Not at all
- Occasionally
- Quite often
- Very often

I have lost interest in my appearance

- Definitely
- I don't take as much care as I should
- I may not take quite as much care
- I take just as much care as ever

I feel restless as if I have to be on the move

- Very much indeed
- Quite a lot
- Not very much
- Not at all

I look forward with enjoyment to things

- As much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

I get sudden feelings of panic

Very often indeed

Quite often

Not very often

Not at all

**I can enjoy a good book or radio
or television programme**

Often

Sometimes

Not often

Very seldom

Appendix W: Fatigue Severity Scale (FSS) scoring sheet

Fatigue Severity Scale

The FSS questionnaire contains nine statements that attempt to explore severity of fatigue symptoms. Read each statement and circle a number from 1 to 7, depending on how appropriate you feel the statement applied to you over the preceding week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement (1 disagree, 7 agree).

During the past week, I have found that:	Score							
1. My motivation is lower when I am fatigued.	<table border="1"><tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td></tr></table>	1	2	3	4	5	6	7
1	2	3	4	5	6	7		
2. Exercise brings on my fatigue.	<table border="1"><tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td></tr></table>	1	2	3	4	5	6	7
1	2	3	4	5	6	7		
3. I am easily fatigued.	<table border="1"><tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td></tr></table>	1	2	3	4	5	6	7
1	2	3	4	5	6	7		
4. Fatigue interferes with my physical functioning.	<table border="1"><tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td></tr></table>	1	2	3	4	5	6	7
1	2	3	4	5	6	7		
5. Fatigue causes frequent problems for me.	<table border="1"><tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td></tr></table>	1	2	3	4	5	6	7
1	2	3	4	5	6	7		
6. My fatigue prevents sustained physical functioning.	<table border="1"><tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td></tr></table>	1	2	3	4	5	6	7
1	2	3	4	5	6	7		
7. Fatigue interferes with carrying out certain duties and responsibilities.	<table border="1"><tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td></tr></table>	1	2	3	4	5	6	7
1	2	3	4	5	6	7		
8. Fatigue is among my three most disabling symptoms.	<table border="1"><tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td></tr></table>	1	2	3	4	5	6	7
1	2	3	4	5	6	7		
9. Fatigue interferes with my work, family, or social life.	<table border="1"><tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td></tr></table>	1	2	3	4	5	6	7
1	2	3	4	5	6	7		

Appendix X: Z Score for Skew and Kurtosis across Variables

Note: Z-Scores of <2.58 ($p>0.1$) can be considered normal

Table 16

*Skew and Kurtosis Z-Scores across all Demographic, Cognitive and Clinical**Variables*

	MS Group		HC Group	
	Skew	Kurtosis	Skew	Kurtosis
Age	-1.97	-0.14	-1.33	-1.06
Pre-morbid	-1.01	-0.99	-1.97	0.88
IQ (WTAR)				
Raw Score				
Anxiety	1.74	0.54	2.19	1.23
Depression	0.38	-1.06	4.18	1.84
Fatigue	-0.44	-0.65	2.45	1.45
CVLT Total	-0.72	0.82	-2.02	-0.39
Raw Score				
SDMT Raw	-0.11	-0.44	1.07	0.27
Score				
Modified	-6.46	2.84	-6.58	2.75
Token Test				
Raw Score				
Arithmetic	0.64	1.25	0.001	-0.59
subtest raw				
score				
Verbal	-0.28	-0.43	-2.19	0.65
Analogies				
Raw Score				
Verbal Series	0.92	-1.07	-1.46	0.53
Raw Score				
TRUSI Raw	-0.22	-0.82	1.04	0.85
Score				

Table 17

Skew and Kurtosis Z-Scores for transformed Depression Variable

	MS Group		Healthy Control Group	
	Skew	Kurtosis	Skew	Kurtosis
SQRT(Depression Raw Score)	-0.79	-0.97	0.83	0.46

Table 18

Skew and Kurtosis across Dependent Variables in Experimental Condition

	MS Group		Healthy Control Group	
	Skew	Kurtosis	Skew	Kurtosis
Massed Recall	2.43	1.26	0.12	-1.10
Spaced Recall	0.001	-0.98	0.29	-1.10
Massed-with- delay Recall	2.2	0.53	0.88	0.21
Massed Understanding	2.0	0.24	-0.87	-0.89
Spaced Understanding	0.49	-0.63	0.89	-0.47
Massed-with- delay Understanding	1.98	0.98	1.35	0.72