



TITLE PAGE

WHAT INFLUENCES ADHERENCE TO TREATMENT IN PEOPLE WITH MULTIPLE SCLEROSIS?

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Abstract

Background

Currently, there are a number of disease modifying therapies (DMTs) available that can help to reduce the number of attacks experienced in relapsing remitting multiple sclerosis (RRMS). However, optimal outcomes are not always achieved due to early treatment discontinuation and low levels of overall adherence. Other research has found a disconnect between studies exploring drivers of adherence behaviour and the body of research that seeks to modify this behaviour, whereby the former is doing little to inform or learn from the latter. This study sought to understand the drivers of nonadherence in people with RRMS from a patient perspective, their potential to be modified through behaviour change intervention and the level of congruence between these two areas of research.

Methods

A two-part scoping review was carried out to determine the drivers of adherence in people with MS and to explore how these drivers are currently being addressed through adherence interventions. The COM-B model for adherence and Behaviour Change Wheel were used to operationalize these findings. Following this review, it was evident that there was a lack of qualitative research exploring drivers of adherence from the perspective of the patient themselves and exploring the 'mechanisms of action' between drivers and behaviour. Therefore, a multi-country, qualitative study was conducted. Semi-structured interviews, based on constructs from the self-regulatory model (SRM) and the COM-B model for adherence were conducted with 24 (n=12 females) people with RRMS from Germany, Spain and the United Kingdom. Framework analysis was used to interpret the data.

Findings

The review identified over sixty discrete factors, across thirty-three studies, which had been found to potentially influence adherence behaviours in MS. Discrepancy between these findings and the COM-B Model for adherence led to creation of a COM-B model specifically for adherence to DMTs in people with MS, which contained eighteen factors, across five of the six categories. The review also identified four successful behaviour change interventions that targeted five of these factors, utilising a total of sixteen behaviour change techniques (BCTs). The qualitative research determined that control and conflict were the overarching themes related to adherence, whereby an increased sense of control over MS and limited conflicts with self-management behaviours and 'day to day' life could enhance likelihood and ability to adhere to treatment and other self-management tasks, thereby leading to potentially better outcomes. These findings also led to revision of the MS specific COM-B model from the first review.

Conclusion

This research has demonstrated that, at this time, there appears to be little congruence between the bodies of research exploring drivers of adherence behaviour in people with RRMS and that which is successfully modifying this behaviour through intervention. A focus on 'convenience' data, in particular clinical and demographic factors, has done little to further our understanding in terms of how best to support this population and there is an apparent need for research exploring drivers of adherence to align more closely with intervention research. This is further supported by the qualitative findings that demonstrated the complex, multi-layered interplay and between drivers and

behavioural outcomes, as well as the influence of individual experiences and beliefs.

Key words: adherence; multiple sclerosis; behaviour change; COM-B model, behaviour change wheel; self-regulation; intervention; scoping review; qualitative

Material in this thesis is the author's, including all figures which are original. Where they represent published data this has been referenced. This copy has been supplied on the understanding that no use of material may be made without proper acknowledgement

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*“There is no exercise better for the heart than reaching
down and lifting people up” John Holmes*

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Background

This scoping review and qualitative research study was undertaken as an independent study within a wider body of work that was sponsored by a pharmaceutical company and is being submitted as part of my Professional Doctorate in Health Psychology Portfolio.

Parts of this work have previously been presented at the European Society for Patient Adherence, Compliance, and Persistence (ESPACOMP) annual conference and the European Health Psychology Society (EHPS) annual conference. In addition, my research informed the design of a patient adherence intervention which has since been rolled out to over 25 countries across Europe.

Scoping Review

Adherence to medication in Multiple Sclerosis: a review of factors impacting adherence behaviours and the interventions to change these behaviours

Introduction

About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, degenerative disease affecting the central nervous system, through demyelination and inflammation. The systemic and uncontrolled nature of the condition results in a variety of symptoms. These symptoms vary in their severity and frequency, both across and within individuals. Symptoms include blurred vision, bladder and bowel dysfunction, fatigue, difficulty with walking and general coordination, and cognitive impairment (Multiple Sclerosis Society UK, 2016).

Who is affected?

MS affects approximately 2.5 million people worldwide, with more women affected than men (2:1). Onset is typically in young adults, with a peak onset age of 30 years, though over the past decade or so there have been an increased number of diagnoses of paediatric MS, with up to 5% of people experiencing the first clinical attack before the age of 16. There is variance in geographical distribution across the world, with prevalence increasing in relation to distance from the equator in both directions (World Health Organization, 2006).

Types of MS

In terms of disease categorisation, approximately 80% of patients are diagnosed with a relapsing-remitting form of the disease (RRMS); characterized by recurring episodes of neurological dysfunction (relapses), followed by periods of full or partial recovery. Over time, the extent of the recovery lessens, leading to progressive disability over the disease course. Of these, 50% will develop secondary-progressive MS within 10 years of onset, which is characterised by progression without presence of relapses. This will increase to 80% of people within 20 years of onset. On average, 10-15% of people will present with primary-progressive MS, which does not feature attacks but has a steady worsening of symptoms. Most people with MS can expect to have a near normal life expectancy (World Health Organization, 2006).

Etiology

There is no definitive etiology known for MS but some of the generally accepted features of the disease provide insight into potential causes and triggers. As described above, the geographical distribution has been investigated to see if there are specific environmental factors involved but no specific cause has been identified, though it is posited that climate plays a role due to the latitudinal dispersion. It is yet to be determined whether this is a direct or indirect cause (World Health Organization, 2006). There are also indications of a genetic component as the risk of developing MS increases for the children and siblings of people already diagnosed (Bennett, 2011). This risk increases in monozygotic twins, further favouring a genetic element, though this is limited to an approximate 30% occurrence rate (World Health Organization, 2006). At a biological level, it is hypothesised that MS is a result

of immune system errors or viral infection. In particular, the presence of the chemical *gamma-interferon* is elevated in people with MS, which may work to increase levels of cytotoxic T cells. These cells 'normally' work to destroy other, damaged, cells. In MS, the T cells seem unable to recognise the myelin sheath of nerve cells of the brain and spinal column as 'part of the self' and therefore seek to destroy them. This may be derived genetically, or there could be a genetic disposition that is then triggered by a viral infection or environmental factor described above (Faith *et al.*, 2013).

Psychosocial Impact

MS has been shown to negatively impact health related quality of life (HRQoL) (Klevan *et al.*, 2014; Mitchell *et al.*, 2005). HRQoL considers the impact of health status on quality of life, in particular going beyond the physical implications to also look at mental, emotional and social functioning (Bullinger, 1991), though research suggests that the physical and psychological components often interact with each other, rather than being separate entities (Wilson and Cleary, 1995). For example, some common MS symptoms such as fatigue, mobility impairments and cognitive problems, can negatively impact many aspects of day-to-day life such as ability to socialise and maintain leisure activities. They can also impact the 'role' of the patient in terms of career and family (Mitchell *et al.*, 2005). These restrictions can then lead to emotional problems, as increasing isolation and the frustration of daily limitations manifest into depression and anxiety (Feinstein *et al.*, 2014).

Even when symptoms are relatively well managed or a person is in a stage of remission, MS patients may still experience poor quality of life, thus demonstrating the need to consider influencing factors beyond the symptom experience. For example, in the early stages following diagnosis, many

patients experience emotional distress, including anxiety, isolation, anger and denial, even though their symptoms and level of disability are relatively mild. Research demonstrates that simply having the label of an 'MS patient' can illustrate a high personal burden (Lysandropoulos and Havrdova, 2015). Several studies have further identified that the emotional distress often experienced by MS patients across the full course of the disease can become so severe that there is a raised risk for long-term psychiatric comorbidities (Marrie *et al.*, 2015; Moore *et al.*, 2015).

As described above, the varying degrees of functional decline and the unpredictable nature of relapses and remission, have a significant impact on the social roles of people with MS and those close to them. In particular, the age of onset occurring in young to middle adulthood has far reaching implications in terms of productivity. Estimates put levels of unemployment in this population as high as 70% (World Health Organization, 2006) with many people unable to continue with their careers following diagnosis (Hakim *et al.*, 2000). In addition, certain health related costs, such as home and transport modifications to accommodate physical disability, often add to these financial challenges (World Health Organization, 2006).

The level of additional care needed, frequently provided 'informally' by family members, means that those close to people with MS can also experience a reduced quality of life (Hakim *et al.*, 2000). This can be related to both the time taken to provide practical support (Buhse, 2008) and the psychological burden that is prevalent amongst informal caregivers in general (Adelman *et al.*, 2014).

Societal Impact

When combined across the MS population, the economic and social implications reach further than the individual and their family and start to represent a significant cost to society as a whole (Trisolini *et al.*, 2010).

The total costs of MS vary across countries for which data are available but are substantial in all countries. A comprehensive report published in 2014, showed the total average cost per person with MS in 2007 varied from a low of \$16,400 (US) in France to a high of \$54,500 (US) in Norway and Sweden. The overall prevalence-weighted average was \$41,000 (US) (Trisolini *et al.*, 2010). Key drivers of this cost can be extrapolated from an analysis conducted for the Australian MS Society that estimated their country's total financial cost per year at \$450m (US), which is the equivalent of 0.07% of their GDP. Some of the key drivers of this cost included informal care, work production losses, hospitalisations and disease burden (Multiple Sclerosis Australia, 2005).

Treatment and Management of MS

Presently, there are no curative treatments available for MS, however there are a number of disease-modifying therapies (DMTs) available that can help to reduce the number of attacks experienced in RRMS. Some therapies are also posited to slow disease progression and modify the overall disease course (Menzin *et al.*, 2013). However as these are more recent forms of DMT, the long-term impact across the lifespan is still to be determined (World Health Organization, 2006).

There are a number of approved DMTs, which vary in their administration method and frequency. Interferon beta treatments are delivered both through

subcutaneous injection (e.g. Betaseron; Rebif) and intramuscular injection (e.g. Avonex). Frequency of administration ranges from once a week to every other day. Other forms of treatment, such as natalizumab (Tysabri), mitoxantrone (Novantrone) and alemtuzumab (Lemtrada) are delivered through infusion, at four-week, three month and yearly intervals respectively. Oral medications were introduced approximately 6 years ago, with fingolimod (Gilenya) being the first, followed by dimethyl fumarate (Tecfidera) and teriflunomide (Aubagio). Dosage is twice a day for dimethyl fumarate and once a day for the others (MS Society UK, 2016b; Menzin *et al.*, 2013; World Health Organization, 2006). Other medications prescribed for MS are used to treat exacerbations or help manage symptoms, such as corticosteroids and analgesics. These are primarily acute in their administration, contrary to DMTs that are prescribed long-term (Menzin *et al.*, 2013).

Treatment Efficacy

The complex nature of MS, including different pathologies, means that response to treatment is variable and can be difficult to predict (Rio *et al.*, 2005; Tomassini *et al.*, 2006; Comi, Radaelli and Sorensen, 2017). Whilst there are some indicators for potential treatment success, such as relatively higher benefits from treatment in early phases of the disease, it is proposed that close monitoring and individualised treatment plans are key to promoting optimal outcomes across the disease course (Comi, Radaelli and Sorensen, 2017). Treatment efficacy can be categorised into 3 overarching outcomes; reduction in relapse rates, reduction in disease progression and MRI (presence of lesions) (Rio *et al.*, 2005). Where treatment is not successful, or stops having a therapeutic effect, then people may be prescribed a number of different treatments / regimens until a response is noted. Even where

treatment is clinically successful, these outcomes can sometimes be difficult for the patient themselves to assess. For example, it can be more difficult for an individual to evaluate the impact of a reduction in disease progression as there is not an immediate effect apparent, potentially leading to uncertainty about the efficacy or need for treatment (Pound *et al.*, 2005).

Treatment Experience

As with the majority of chronic conditions, treatment of MS requires a long-term commitment from the patient to adhere to the treatment regimen as prescribed (Lugaresi *et al.*, 2012). As described above, DMTs prescribed for RRMS work to reduce the number of relapses experienced or to delay the progression of disability, rather than providing relief for day-to-day symptoms (Menzin *et al.*, 2013). Research has described the low levels of treatment satisfaction people with MS experience, related to factors such as the inconvenience of methods of delivery (in particular with injection and infusion-based treatments), difficult dosing schedules and the presence of significant side effects (Klauer and Zettl, 2008; Twork *et al.*, 2007). These factors have been indicated as contributing to the levels of non-adherence seen in this population (Glanz *et al.*, 2014).

Why adherence is important

Generally, with long-term treatments for chronic conditions, it is understood that sub-optimal adherence rates and levels of premature discontinuation by the patient are high, with a figure of approximately 50% being proposed across conditions (Sabaté, 2003). The publication of three high-profile reports in 2003 demonstrated the increasing level of attention that was being placed on the problem of adherence at the time (Carter, Taylor and Levenson, 2003; Harrison, 2003; Sabaté, 2003) and which still continues to be a focus of

healthcare research and guidance (Hazell and Robson, 2015; Sav *et al.*, 2015; NICE, 2009). Between them, these reports highlight the far-reaching impact of non-adherence. They claim that poor adherence is the biggest 'threat' to the potential clinical benefits of treatment. These are reflected as medical and psychosocial complications, and the subsequent impact on an individual's quality of life (Carter, Taylor and Levenson, 2003; Harrison, 2003; Sabaté, 2003).

There is also the need to consider the waste of medicines and additional utilisation of healthcare resources that could be directed elsewhere (Sabaté, 2003; Hazell and Robson, 2015). These economic considerations are of particular importance as we are in a stage of ever-increasing health costs; both in terms of the prevalence of chronic, lifelong conditions and the rising prices of prescription treatments (Kesselheim, Avorn and Sarpatwari, 2016; Iuga and McGuire, 2014). For example, in the US it is estimated that healthcare costs will account for 20% of Gross Domestic Product (GDP) by 2020, and that 20-30% of this cost will be classified as 'wasteful' spend (Iuga and McGuire, 2014). Non-adherence is a considerable contributory factor to this, with estimate annual costs of \$100 – \$300 billion in the US (IMS Institute for Healthcare Informatics, 2013) and €1.25 billion in the EU (European Patients' Forum, 2011). These costs are represented by direct medicine value, avoidable hospitalisation, and increased health service utilisation such as primary care visits and emergency room admissions (Iuga and McGuire, 2014).

A further consideration is the broader societal impact, caused by absenteeism and reduced productivity as a result of poorer health outcomes. Whilst these factors are considerations for living with a chronic disease in general, it is posited that they are exacerbated further due to inappropriate medicines usage (Benjamin, 2012; Loeppke *et al.*, 2009). These 'costs' are not factored into the estimates given above, demonstrating the ever increasing economic and social impact when a condition is not properly managed (Loeppke *et al.*, 2009).

Non-adherence in MS – what is happening?

This impact and cost of non-adherence are also replicated in MS. For example, clinical outcomes such as the presence of higher rates of relapse, disease progression, and hospital visits and hospital stays increase in MS patients who demonstrate less adherence (Girouard and Soucy, 2011; Halpern *et al.*, 2011). Similarly, on an economic level, non-adherence is linked to higher medical costs (Tan *et al.*, 2011; Steinberg *et al.*, 2010).

Much of the literature on adherence in MS focuses on DMT regimens (Menzin *et al.*, 2013) as these are frequently prescribed longer term and represent an attempt to positively influence the course of the disease, as opposed to acute, symptom management treatments (MS Society UK, 2016a). Therefore, it is the non-adherence to this range of treatments that poses the largest threat to long-term outcomes for patients and the healthcare system in general (Menzin *et al.*, 2013).

Two main types of adherence data have informed the current literature on MS. Persistence; defined as the time from treatment initiation to discontinuation or

significant gap (e.g. 30 days) and reported as a percentage of patients and adherence; defined as the percentage of doses taken as prescribed over a period of time by an individual (Menzin *et al.*, 2013).

Risk of treatment discontinuation tends to be greatest in the first 6 months of therapy, with studies showing up to 27% of patients stopping in this time. This coupled with evidence of discontinuation rates reducing post 6 months, suggests that this is a crucial time period for establishing long-term persistence (Tremlett and Oger, 2003).

Research also demonstrates that adherence to DMTs is variable, with a review conducted in 2013 finding adherence rates ranging from 41% to 88% of doses being taken (Menzin *et al.*, 2013). Some of this variation could be attributed to disease related factors, such as treatment type and course of MS, but it is suggested that study type and the definition of non-adherence used also contribute to the level of variation in the data (Menzin *et al.*, 2013; Klauer and Zettl, 2008).

Non-adherence in MS – why is it happening?

Understanding the levels of non-adherence is important but research in this area also seeks to understand what the causes of non-adherence are. It is recognised that in a healthcare system that needs to support people to better self-manage, there needs to be a greater understanding and consideration of the needs and preferences of patients (Vermeire *et al.*, 2001).

Terminology

Described above is the type of data used to inform adherence studies, but in terms of terminology, there has been much debate about the appropriate language to use when talking about medicines use (and in fact, undertaking general health / self-management behaviours overall) (Vermeire *et al.*, 2001). This is an important debate as it is hypothesised that the language used goes beyond simply describing the activity to being representative of the overall 'ideology' surrounding this concept of 'adherence' and the suitability of terms to appropriately represent the role of the patient themselves (De las Cuevas, 2011)

Compliance

Compliance is a term that is seen currently as 'unfavourable' due to the implication that the patient 'role' in this scenario is a submissive one and that non-compliance is actually a failure or unwillingness to do as instructed. In this scenario, the fault firmly lies with the patient themselves as it is based on assumption of absolute authority and correctness on behalf of the healthcare system making the recommendations (De las Cuevas, 2011).

Concordance

This term was introduced by the Royal Pharmaceutical Society in response to a recognition that a one-dimensional approach to medicine taking was not cognizant with an evidently complex and pervasive phenomenon (Blenkinsopp, Bond and Britten, 1997). Originally, this term placed the patient as a decision maker alongside their healthcare professional and tries to shift the focus to the desired outcomes of a treatment regimen for the patient, rather than just the 'best' clinical decision of the doctor. This terminology indicates a partnership, so the role of the physician must also change to one

of empathy and listening to the outcome goals of the patient (Blenkinsopp, Bond and Britten, 1997). Over time, this term has become even broader, covering a wide range of topics around general patient support with medicine taking (Horne, Weinman, Barber 2005).

Adherence

The term adherence is defined as ‘the extent to which the patient’s behaviour matches agreed recommendations from the prescriber’ – so once again moving away from the patient as a passive entity towards one where their agreement is seen as key to the medicines taking process (Horne, Weinman, Barber, 2005).

So, when we seek to understand ‘why’ non-adherence is occurring, insight into the implications of the rhetoric surrounding the research in this area is important as it provides the lens from which the behaviour is being viewed. However, it is also important to consider the way that research is being conducted. For example, a study may refer to concordance, but if the hypothesis or measures still infer compliance to prescribed regime as the goal, without, for example, looking at how involved a patient was in the decision-making process, then can it really be said to be exploring concordance?

Across the literature, these terms are often used interchangeably and unfortunately not always accurately (De las Cuevas, 2011). To this end, for clarity in this thesis the term adherence is used to reflect the overall concept of medicine taking, with specific behaviours (e.g. number of doses, discontinuation) referred to where applicable to detail the specific behaviour being studied.

Intentional and unintentional adherence

Studies across chronic conditions have shown that poor adherence can be the result of both deliberate and unintentional behaviour. For example, patients may take a lower dose than is recommended following consideration of the treatment and making a deliberate (intentional) decision to alter the dosage or take a drug holiday (Pound *et al.*, 2005). Alternatively, they may alter their medication dosage unintentionally, as a result of misunderstanding the instructions they have been given, or forgetting (Horne *et al.*, 2005).

Identification of and the reasons behind both forms of adherence behaviour need to be understood and addressed in order to tackle non-adherence and offer effective patient support (Horne *et al.*, 2005).

Intentional – illness perceptions

In the general population, it is acknowledged that the beliefs an individual holds about their illness and their treatment can have a significant impact upon their ability to adjust to and cope with a condition, both in terms of appropriate self-management behaviours and emotional wellbeing. These beliefs form the basis of a theoretical model proposed by Leventhal and colleagues, the Self-Regulatory Model (SRM) (Leventhal, Meyer and Nerenz, 1980), also referred to as the Common-Sense Model of Self-Regulation (CSM) (Leventhal, Phillips and Burns, 2016). The SRM is a multi-level, conceptual framework that examines the perceptual, behavioural and cognitive processes that are involved in the self-management of health threats. The model proposes that individuals will appraise the potential threat posed from an illness and form both cognitive and emotional responses to the illness threat. The threat can be somatic sensations (e.g. symptoms), function

deviations (e.g. a fall) or can be socially presented (e.g. a doctor's diagnosis, public health campaign).

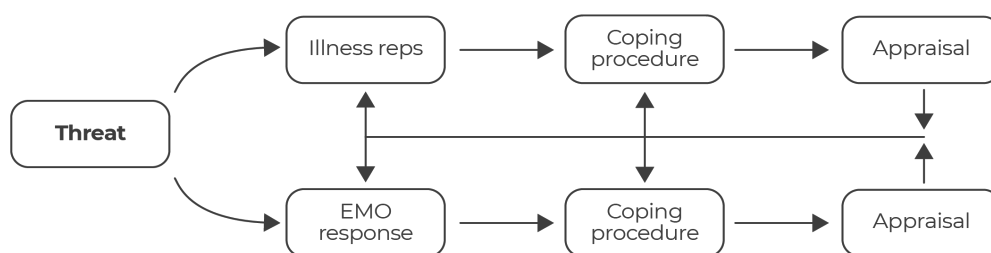
These stimuli will then activate both memory structures relating to past illness experiences and what 'normal' functioning is, and then cognitive representations of the threat that are the current appraisal (Leventhal, Phillips and Burns, 2016). Evidence from across multiple chronic conditions shows that patients form representations relating to five key variables: the *cause* of the illness, its *nature* or identity, its *duration*, the *personal consequences* of suffering from it and the extent to which the illness can be *controlled* or cured (Moss-Morris *et al.*, 2002).

It is these memories and representations that dictate the strategies an individual will use to cope with the threat. In this way, the SRM is a framework that allows for the categorisation and understanding of the processes underlying the initiation and maintenance of health self-management behaviours (e.g. adherence, lifestyle change). A key feature of this is the recognition that this process is multi-level and dynamic. For example, rather than just having dichotomous factors of perceived seriousness and vulnerability, such as in the Health Belief Model (Rosenstock, Strecher and Becker, 1988), it seeks to break this threat into its component parts (the levels). What are the immediate consequences, what are the predicted future consequences, how controllable is it, how long will it last? How much does this experience replicate / differentiate from previous health threats? What coping strategies have worked before, what is within my power to do? It is in this way that it is dynamic as it recognises that different combinations of these will elicit different responses. The model also accounts for change overtime as different experiences form new memories and appraisals of the

effect of coping strategies are assessed for their ability to remove or moderate the health threat (see Figure.1). In this way, the framework provides an opportunity to not only predict behaviours but to understand the dynamic processes leading to action (or inaction) and therefore can provide targets for intervention (Leventhal, Phillips and Burns, 2016; O'Connor, Jardine and Millar, 2008; Leventhal, Meyer and Nerenz, 1980).

There is further evidence of the role of these beliefs in specific relation to medicine taking behaviours, which are considered part of the coping response within the SRM (Leventhal, Phillips and Burns, 2016). A decision about treatment will be rational if it fits with the patient's own beliefs about the illness and the appropriate treatments for it, even when the decision is at odds with the professional healthcare advice given (Horne and Weinman, 1999). Studies have demonstrated that these beliefs can predict the likelihood of adherence behaviours in a number of conditions including asthma, diabetes, heart failure and hypertension (Kucukarslan, 2012).

Figure 1 – Self-regulatory model (Leventhal, Meyer and Nerenz, 1980)



Key:
 SRM

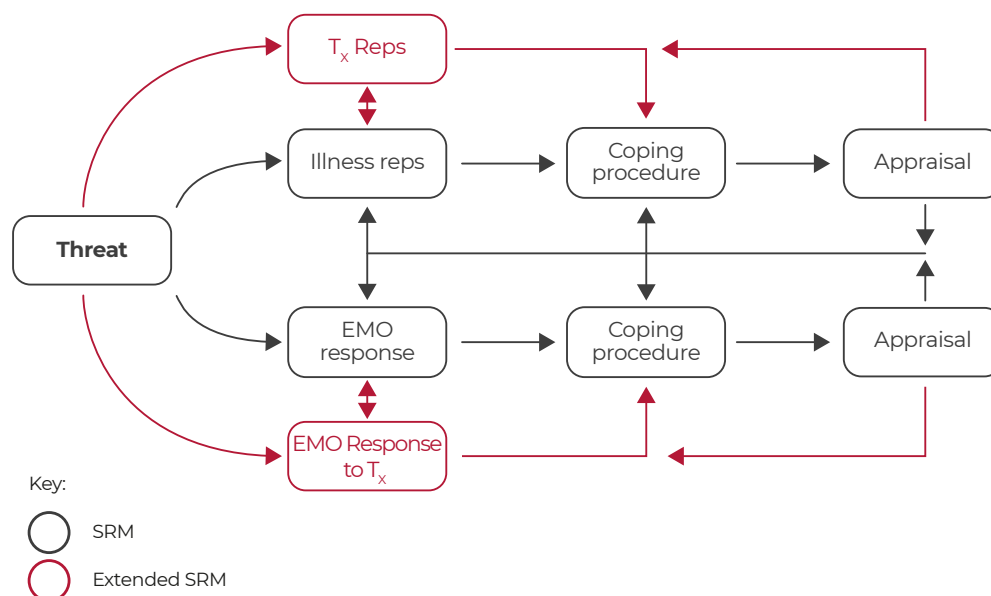
When considering illness perceptions in MS, it is possible to see how the nature of the condition could impact an individual's illness perceptions, and in turn the coping behaviours that someone undertakes. For example, illness identity (in terms of symptom experience and attribution) is seen as key catalyst for prompting action in both acute and chronic conditions (Moss-Morris et al., 2002). The fluctuating nature of symptoms in RRMS, means that in periods of remission, people may reduce their activity in terms of disease management as they perceive it to be dormant or simply don't have the somatic cues to prompt action. The unpredictable course of the condition can impair beliefs around how much control an individual has over their MS. Low personal control, in turn, can reduce the likelihood of engaging in coping behaviours, related to a sense that there is little that can be done (Wallston and Wallston, 1978).

Intentional – treatment beliefs

In addition to illness perceptions, with regards to adherence there is also evidence of the role of individual treatment beliefs in determining behaviour. These 'common-sense evaluations' of prescribed medicines are grouped into two categories: perceptions of the need for treatment (necessity beliefs) e.g. in the absence of symptoms, and concerns about a range of potential undesired outcomes, e.g. side effects, addiction. This is referred to as the 'Necessity-Concerns Framework (NCF)' and it is proposed that patients perform a "cost-benefit" analysis, weighing-up possible benefits and risks of taking medication (Horne, Weinman and Hankins, 1999). A meta-analysis of 94 studies exploring the impact of these beliefs on adherence behaviour demonstrated a significant impact of both necessity and concerns beliefs on adherence, even when controlling for study size, country and the adherence

measure used (Horne *et al.*, 2013). Leventhal and colleagues (2016) propose that there is a strong interplay between illness and treatment representations and incongruence between the two can impact behavioural outcomes. As per the earlier example, a lack of or reduction in somatic symptoms experienced in a period of remission may reduce the perceived necessity for treatment. A representation that DMTs should quickly relieve symptoms (identity, timeline) may lead to concerns about treatment efficacy when symptom relief is not experienced. Therefore, consideration of both illness and treatment representations should be taken when exploring adherence (Leventhal, Phillips and Burns, 2016). Figure 2 shows an ‘extended’ self-regulatory model to include treatment representations.

Figure 2 – ‘Extended’ Self-regulatory model (Leventhal, Phillips and Burns, 2016)



Unintentional – neuropsychological symptoms

Cognitive dysfunction is a common problem in people with MS, linked to damage caused by MS related lesions on the brain. The manifestation of these problems is heterogenous, with symptoms, severity and speed of

decline varying greatly between patients (Mohr and Cox, 2001). Problems with memory and executive function (e.g. problem solving, sequencing) can negatively impact an individual's ability to adequately adhere to treatment regimens. Memory problems may lead to forgetting to take treatment as prescribed and reduced executive function may, in turn, reduce the ability for the individual to be able to formulate or put in place ways to mitigate memory problems, such as setting reminders. More broadly, if we consider that the self-regulatory model is contingent on cognitive processes (i.e. representations, action planning, coping appraisals) then we can see how the threat itself (MS) can be not only the trigger for self-management behaviours but may also be impeding the process of self-regulation.

Modifying behaviour

Of particular note with regards to illness and treatment representations is not only their utility to predict adherence behaviours but their modifiability also. Evidence shows that interventions to address 'unhelpful' beliefs can change not only the perceptions themselves but that that change can translate into health behaviours and outcomes too (Broadbent *et al.*, 2009; Petrie *et al.*, 2002). For example, an SMS text-based intervention in asthma was successful in changing illness perceptions, treatment beliefs and adherence behaviours, with the changes sustained after the intervention had ended (Petrie *et al.*, 2012). This demonstrates the potential of interventions that are designed to change these underlying, belief-based drivers of adherence to be relatively short whilst still impacting long-term behaviour (Petrie *et al.*, 2012; Broadbent *et al.*, 2009). This is in contrast to other interventions whereby taking the support away often leads to a reversion of behaviour, for example reminders, contingent rewards and financial support (Nunes *et al.*, 2009). The importance of deliberate non-adherence and the contribution of patient beliefs

are highlighted in recommendations concerning adherence produced by the National Institute for Health and Care Excellence (NICE, 2009).

COM-B Model

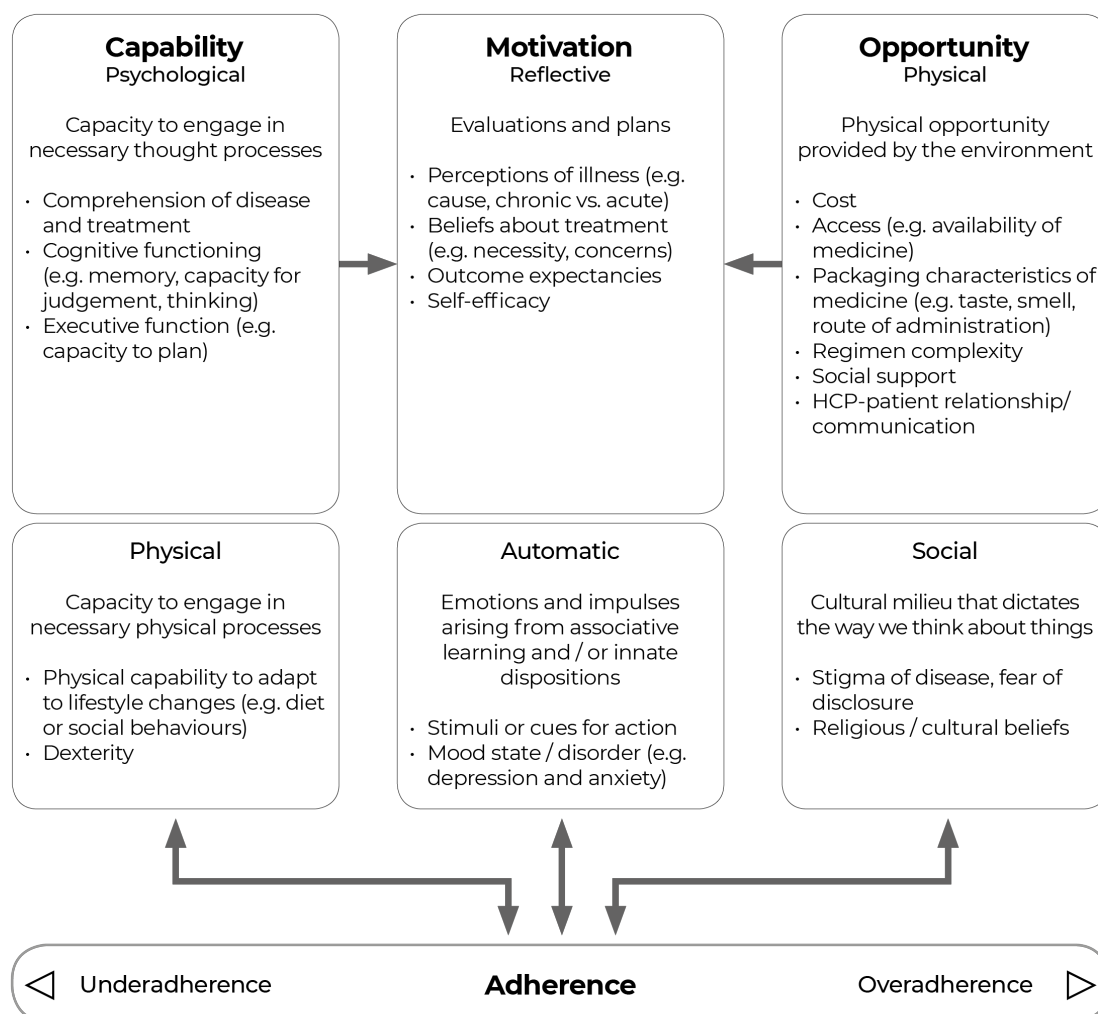
However, whilst the evidence and the importance of the role of illness and treatment beliefs in adherence is undoubtedly strong, these beliefs do not occur in isolation and will be impacted by other medicine and illness related considerations, as well as varying according to disease type, treatment type and individual experiences. To this end, it is important to consider these beliefs in the context of the overall treatment and illness experience. One such way to do this is through the utilisation of the Capability, Opportunity and Motivation model of behaviour (COM-B) (Michie, van Stralen and West, 2011). The model proposes that health behaviours are driven or limited by a range of factors which can be grouped under three broad categories: a person's Capability (e.g. reduced cognitive function, lack of understanding, mobility limitations), Motivation (e.g. illness perceptions and treatment beliefs as described above, depression, anxiety) and Opportunity (e.g. social support, health care system factors). As well as each component influencing adherence directly, opportunity and capability may also affect motivation, thus moderating / mediating behaviour this way (Michie, van Stralen and West, 2011). A review by Jackson and colleagues has applied this model specifically to adherence behaviours (Jackson *et al.*, 2014). Figure 3 shows the sub-components proposed to influence adherence identified from their review.

As described above, when we examine these sub-components in the context of MS, capability factors such as executive function may not only impact adherence directly through reducing planning ability, but, if it is interfering with the self-regulation process as well, then this may be influencing the illness

and treatment representations which sit within the category of motivation.

However, COM-b also starts to help us think about the broader context of the MS patient. What level of support are they receiving to manage the impact of the disease? How good is their relationship with the healthcare team, and what influence is this having on their understanding and trust of self-management recommendations?

Figure 3 – COM-B Model for adherence (Jackson et al., 2014)



Whilst the SRM helps us to understand the cognitive processes in place, COM-B gives a framework to define further what may be influencing these processes or where people may experience barriers to ‘action’ (e.g. access to medicines (opportunity, physical) or physical ability to self-inject (capability,

physical)). Additionally, whilst it is proposed there is an emotional processing response alongside the cognitive one, this is specific to emotions 'prompted' by the illness and are discreet from more global mood disorders, such as depression and anxiety (Moss-Morris et al. 2001). COM-B allows for consideration of both, and therefore the different ways they may be impacting adherence (Jackson *et al.*, 2014). This differentiation and 'next layer' of definition is important as not only does it deepen our understanding but also helps to form the basis for behavioural intervention (Jackson *et al.*, 2014).

Designing interventions

As with the understanding of influencing factors, an important consideration for intervention design is the use of theories of behaviour and behaviour change. In the UK, the Medical Research Council (MRC) recommends an analysis of theories before intervention testing to understand the likely processes and drivers of change (Campbell *et al.*, 2007). However, there are conflicting results across literature as to how consistent the difference is between those using a theoretical underpinning and those not, with positive and negative results being found for both types of intervention (Michie, Atkins and West, 2014). It is proposed however that this is likely related to methodological issues, namely how the theory is understood and applied, and also how it is reported in relation to the intervention description, rather than an indication of a lack of effectiveness. It is suggested that, if applied and utilised appropriately, theory may lead to more effective interventions (Michie, Atkins and West, 2014).

Health related behaviours are complex; as mentioned above they do not occur in a vacuum. Psychological, social, cultural, clinical and economic relationships and processes can all influence the performance of health-

related behaviours (Ogden, 2016). It is proposed that a theory can provide a systematic framework for identifying not only the antecedents of behaviour (Michie, van Stralen and West, 2011) but also provide an opportunity to explore these in the context of incidental and mediating factors thereby 'shining a light' on the range of influencers to be considered and / or addressed through the intervention (Rothman, Sheeran and Wood, 2009; Rothman, 2004).

The reciprocal relationship between theory and intervention also means that the application of theory to intervention design allows for evaluation and, where applicable, refinement of that theory through its practical application (Abraham and Michie, 2008; Rothman, 2004).

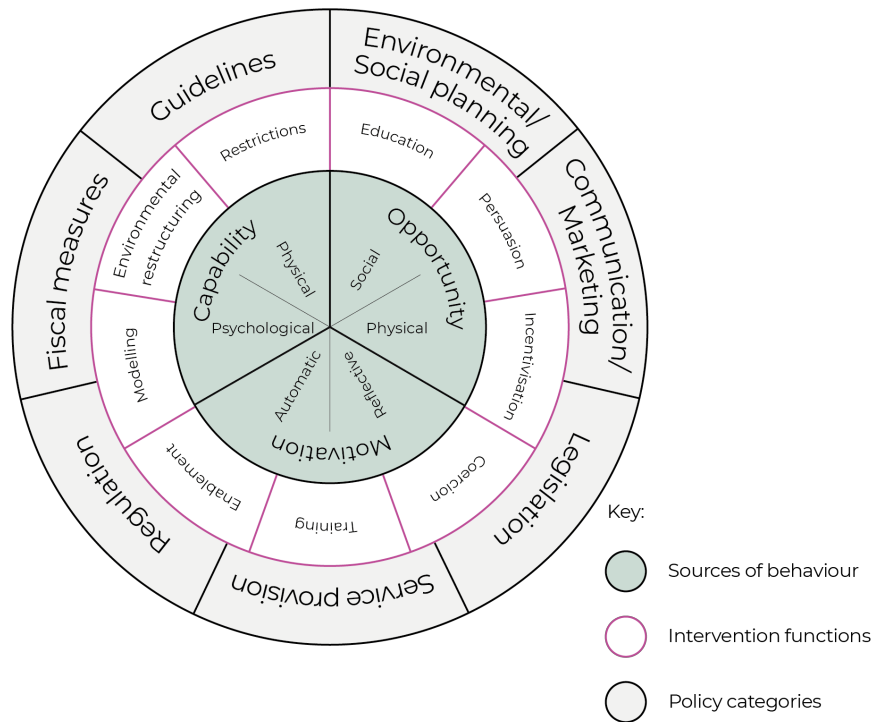
However, despite these apparent advantages, a review of implementation research in 2010 estimated that only about 20% of studies utilised a behaviour change theory (Davies, Walker and Grimshaw, 2010). Furthermore, studies, which apply the theory systematically, are even more limited, with the majority simply referencing a theory as influential rather than detailing how the constructs map specifically onto intervention components (Webb *et al.*, 2010).

Behaviour Change Wheel

The Behaviour Change Wheel (BCW, see Figure 4) is intended to provide a systematic way to design behavioural interventions that allows for theoretical underpinnings to be applied in a way that not only explains behaviour but allows for consideration of how to change it. The COM-B model (described above) provides the centre point but the next layer of the wheel explores ways in which the factors identified as influencing behaviour may be targeted, either to promote facilitating factors, or remove potential barriers through the

identification of appropriate intervention functions, policies to support intervention execution, the application of discreet behaviour change techniques (BCTs) and selection of mode of delivery (Michie, Atkins and West, 2014).

Figure 4 – Behaviour Change Wheel (Michie, Atkins and West, 2014)



Intervention Functions

Once the behaviour has been better understood in terms of what needs to be changed to influence it through COM-B, the next stage as proposed by the BCW is to identify intervention functions, namely the type of intervention that can be applied to address specific behavioural categories, that will be effective to bring about the desired changes. There are 9 intervention functions described in the wheel; education, persuasion, incentivisation, coercion, training, restriction, environmental restructuring, modelling and enablement. It is proposed that these functions map specifically to particular COM-B

categories. For example, educational interventions can influence physical capability and reflective motivation, whereas persuasion can influence automatic and reflective motivation.

Policy Categories

The next layer of the BCW promotes identification and understanding of the policies / supporting functions that can be used to deliver intervention functions. For example, communication / marketing can help deliver education and incentivise people to take action. To support an intervention function of environmental restructuring, environmental / social planning policies may need to be deployed. Seven policies are described within the BCW; communication / marketing, guidelines, fiscal measures, regulation, legislation, environmental /social planning and service provision. As with the intervention functions, there is a proposed mapping of these policies to functions, to aid intervention design (Michie, Atkins and Gainforth, 2014).

Behaviour Change Techniques

Once the appropriate considerations have been mapped out for the overarching intervention functions and supporting policies needed to put an intervention in place, the specific components of that intervention then need to be created. Approaches that have been used to target health behaviours have been brought together through review and consensus as part of an overarching taxonomy of behaviour change techniques (BCTs) (Michie *et al.*, 2013; Michie *et al.*, 2011b). Intervention functions may be delivered through multiple BCTs. For example, education may consist of 'information about health consequences' and 'instruction on how to perform the behaviour'. Currently, the taxonomy describes 93 techniques that can be used to attempt to change behaviour, grouped into 16 overarching categories (Michie *et al.*,

2013). The taxonomy has been applied to understanding and mapping effective methods of change for a range of health-related behaviours, including healthy eating and physical activity (Michie *et al.*, 2011a) smoking cessation (Michie *et al.*, 2011b) and reduced alcohol consumption (Michie *et al.*, 2012).

Mode of Delivery

The final step is choosing the mode(s) for the execution of the intervention, usually informed by practical considerations, such as location, type of population and availability of budget and resources.

Impact of approach

The BCW has been used in a number of areas, both through utilisation of discreet parts of the wheel to increase understanding (COM-B and BCT studies as described above) and in full to help turn insights into action, for example provision of contraception to adolescents (Rubin, Davis and McKee, 2013), understanding use of risk assessment strategies in cardiovascular practice (Bonner *et al.*, 2013) and implementing evidence-based guidelines for premature babies (Crowther *et al.*, 2013).

However, even with these systematic strategies being put in place and some evidence of their feasibility, the relative impact of health behaviour change interventions is fairly low and inconsistent, suggesting there may be more to be done and / or understood (Bull *et al.*, 2014; Kripalani, Yao and Haynes, 2007; McDonald, Garg and Haynes, 2002; Haynes, McKibbin and Kanani, 1996).

Within the area of adherence, a suggested reason for this is the apparent disconnect between the research priorities of those providing healthcare and

the needs of those consuming it, particularly the focus on consumption of pharmaceutical products (Pound *et al.*, 2005). Whilst 'professionals' (including physicians, researchers, policy makers) may see medicine taking as something that should simply be done 'as prescribed', leading to monitoring of compliance and related variables in a fairly 'quantitative' way (Vermeire *et al.*, 2001) individuals see medicines as a resource that they use 'as and when' to support the overall management of their condition (Pound *et al.*, 2005; Blaxter and Britten, 1996). As discussed previously, this is writ large in the case of describing 'adherent' behaviours.

A further explanation for this apparent 'lack of success' (Pound *et al.*, 2005) could be the chasm between the research that looks at the 'why' of nonadherence and the research that seeks to change adherence behaviour (Allemann *et al.*, 2016). For example, a recent review on adherence to oral antiplatelet therapy in people with Acute Coronary Syndrome, found that studies which looked at reasons for non-adherence primarily explored demographic, clinical and treatment variables. Yet the handful of successful interventions primarily targeted psychosocial variables, such as emotional wellbeing, treatment perceptions and relationship with healthcare professionals (Johnston *et al.*, 2016).

Turning insights into action

As described above, the potential of DMTs to improve outcomes for people with RRMS and the wider reaching socioeconomic implications of non-adherence means that understanding how to increase and maintain adherence certainly warrants exploration. However, whilst some research has sought to identify factors impacting adherence and persistence in MS

(Devonshire *et al.*, 2011) and other studies have reviewed behaviour change interventions in people with MS (Roche, McCarry and Mellors, 2014) there are currently no published reviews in MS looking at the extent to which factors identified as influencing adherence to DMTs have also been successfully modified through intervention. It is proposed that a greater cohesion between these two elements may provide an opportunity to 'refocus' research aims onto variables that provide the greatest opportunity for change (Allemann *et al.*, 2016).

Therefore, this two-part scoping review will explore this relationship by: identifying the most prolific patient-related factors found to be influencing adherence to DMTs; reviewing behaviour change interventions in MS to see which of these identified factors have been subsequently targeted through intervention and, crucially, also demonstrated effectiveness through improved adherence outcomes.

Specifically, the aims of this review are:

- To determine the factors that have been identified as influencing adherence to prescribed DMTs in people with MS
- To operationalize the identified factors using the COM-B model of behaviour change as applied to adherence to allow for comparison across studies and understand the applicability of the model for this population
- To determine which of these factors have been successfully modified through intervention, and how

- To categorise the successful intervention components using the BCW to allow for comparison across studies and understand how / if the interventions align with suggested links within the BCW
- To explore the degree of consistency between the factors identified through research and those targeted and subsequently modified through intervention
- To understand current gaps in our knowledge relating to adherence in MS

It is hoped that this review will help to rationalise the factors that have been shown to influence adherence in MS to those that have demonstrated response to behavioural intervention and to highlight the amount of congruence or disparity between research exploring adherence drivers and adherence interventions in MS.

Methods

A scoping review methodology was chosen to identify and review the literature. A scoping review, whilst still following a 'systematic' approach, aims to rapidly map the key concepts from a particular research area. A scoping review still seeks to understand the breadth of the research available but does not go into the depth of detail of a traditional Systematic Review. In practical terms this means the data extracted is focussed more explicitly on the research questions (as opposed to extracting all the variables) and there is less focus on the quality and relative 'weight' of the findings (Arksey and O'Malley, 2005).

In their case study paper, Arksey and O'Malley (2005) describe four primary reasons for selecting a scoping methodology, one of which is to identify current gaps in knowledge in a particular research area. In terms of this review the primary purpose was to identify to what extent two fields of adherence research in MS compare in terms of their findings and focus (Arksey and O'Malley, 2005). As described above this methodology is systematic, allowing for transparency and replication. A systematic approach is also important as it increases the reliability of the findings and including clear methodological and data descriptions allows for findings to be viewed and understood in context (Petticrew and Roberts, 2008; Mays, Roberts and Popay, 2001).

A scoping review follows the same process as a systematic review in terms of identifying and selecting studies for inclusion (Petticrew and Roberts, 2008; Arksey and O'Malley, 2005) and a description of the process for this review is provided below. The key difference is in the charting of the data. As

mentioned, there is no quality assessment and it deliberately seeks to extract and present only the data that is the most pertinent to the research question and relatively easy to understand. In this respect it mirrors a narrative review methodology (Pawson, 2002). To aid the understanding of the data it is recommended that a common and 'logical' framework is applied to how the findings are presented (Arksey and O'Malley, 2005; Pawson, 2002). The framework for this review is also described below.

Review 1: Factors impacting adherence in MS

Systematic literature searches were conducted using CINAHL, Medline, PsychArticles, PsychINFO (via EBSCOHost) and the Cochrane Register for Controlled Trials and Systematic Reviews. The search terms used across all databases are summarised in Table 1. Subsequently, the reference lists of articles that were included at data extraction stage were examined to identify any relevant articles that may have not been returned in the database search.

Table 1: Factors impacting adherence to treatment in MS - Search Terms

1	(adherence* OR complian* OR initiat* OR persist*) AND ("M.S." OR "multiple sclerosis")
2	(adherence* OR complian* OR initiat* OR persist*) AND ("M.S." OR "multiple sclerosis") AND (relaps* OR remit*)
3	(adherence* OR compliance* OR initiat* OR persist*) AND ("M.S." OR "multiple sclerosis") AND inject*AND oral*

Literature was limited to those written in the English language and published after January 1st, 1994. This date was chosen as the first licensed DMT for RRMS was approved in 1993 and therefore only clinical trial, as opposed to real world, data would have been available prior to this. Additional inclusion criteria required that studies involved people diagnosed with MS who were prescribed medicines for the management of MS and described patient provided reasons for non-adherence / discontinuation or patient related correlational data between factors and non-adherence / discontinuation. Studies were excluded if they only examined physician led clinical decisions for discontinuation, as the focus of this research was patient related factors. As appropriate for a scoping review, no limits were put on the type of study design as the purpose was to understand the range of factors impacting adherence, including those related to the patients' lived experiences and their own commentary, not necessarily the most frequent or strongest predictors (Arksey and O'Malley, 2005). Review and commentary papers were excluded, as it was preferential to examine the original studies to extract the data specific for the research question.

Similarly, as this was not a systematic review, a formal quality assessment was not conducted to determine inclusion / exclusion, but overarching quality and design implications and observations were noted as part of the review process and are included in the discussion to provide context.

A total of 4,874 abstracts were identified through the search methodology of which 4,804 were eliminated through a title search, leaving 70 abstracts to be checked. At this stage, a further 19 were excluded, leaving 51 full texts to be

read. Full text review eliminated a further 20 studies, leaving 31 papers for data extraction. These papers also had their reference lists checked. The reference list check identified 5 possible additional papers, 2 of which were subsequently included, resulting in 33 papers included in the main review. The complete process flow for study selection, including reasons for exclusion can be found in appendix i.

For each study included in the final review the following data were extracted: study type, collection methods, sample size, type and definition of 'adherence' measured and statistically significant or patient elicited factors impacting nonadherence. These data were believed to be sufficient to give context to the primary findings.

Review 2: MS Adherence factors successfully modified through intervention

A relevant scoping review was identified early on in the research process that had explored interventions and their components to support self-management behaviours in MS; this included the specific identification of interventions for medication adherence (Plow, Finlayson and Rezac, 2011). To this end, the systematic search strategy was modified to identify studies published post the review timeframe (2008 onwards). The same databases were searched as for the factors review above and the search terms used are summarised in Table 2.

For consistency, inclusion / exclusion criteria were followed in line with the factors review above and those applied to intervention definition from the scoping review (Plow, Finlayson and Rezac, 2011). To this end, literature was limited to those written in the English language and involved people diagnosed with MS who were prescribed medicines for the management of MS. Studies needed to describe the intervention in a way that allowed for specific intervention components to be identified and evaluation of the outcomes of the intervention. Studies were excluded if they were case studies or single-subject design as an objective of the research was to help rationalise the research to aid intervention focus and therefore interventions that had been applied at a population level were deemed more relevant to this aim. Studies were also excluded if they described education only interventions (see Plow, 2011 for a definition) as whilst information provision and providing core education are a key part of enabling self-management, it is widely recognised that education alone is not enough to change behaviour (Haynes *et al.*, 1996).

Non-impactful studies were also excluded to aid rationalisation of findings into those which could help inform future research and intervention design focus.

Table 2: MS Adherence factors successfully modified through intervention -

Search Terms

1	(intervention*) AND (multiple sclerosis* OR M.S.*) AND (self-manag* OR adher*)
2	(intervention*) AND (multiple sclerosis* OR M.S.*) AND (relaps* OR remit*)
3	(intervention*) AND (multiple sclerosis* OR M.S.*) AND (self-manag* OR adher*) AND (digital OR technolog* OR mobil* OR web* OR internet* OR online* OR app*)

A total of 361 abstracts were identified through the search methodology of which 315 were eliminated through a title search, leaving forty-six abstracts to be checked. At this stage, a further thirty were excluded, leaving sixteen full texts to be read. Full text review eliminated a further fourteen studies, leaving two papers for data extraction. These papers also had their reference lists checked but no additional studies were found. Of the twenty-seven that were included in the scoping review by Plow et al. (2008), two met the inclusion criteria and were included in the final review papers. The complete process flow for study selection, including reasons for exclusion can be seen in appendix ii.

For each study included in the final review the following data were extracted: study type, collection methods, sample size, type and definition of 'adherence' measured, adherence factors targeted, BCTs applied and significant

adherence outcomes¹. As with the first review these data were believed to be sufficient to give context to the primary findings.

Findings

Review 1: Factors impacting adherence to treatment in MS

Overview

The total sample size across the studies was 20,162 (range 30 - 4,111; mean 610). Of the thirty-three studies included in this review, twenty-three were prospective studies (Jongen, Wim and Boringa, 2016; Turner *et al.*, 2016; Warrender-Sparkes *et al.*, 2016; Wicks *et al.*, 2016; Glanz *et al.*, 2014; Hupperts *et al.*, 2014; Lulu *et al.*, 2014; de Seze, Borgel and Brudon, 2012; Koudriavtseva *et al.*, 2012; Lugaresi *et al.*, 2012; Beer *et al.*, 2011; Hancock, Bruce and Lynch, 2011; Bruce *et al.*, 2010; Treadaway *et al.*, 2009; Turner *et al.*, 2009; Siegel, Turner and Haselkorn, 2008; Tremlett *et al.*, 2008; Turner *et al.*, 2007; Daugherty *et al.*, 2005; Rio *et al.*, 2005; Fraser *et al.*, 2004; Mohr *et al.*, 2001) and ten were retrospective (Fernández *et al.*, 2016; He *et al.*, 2015; Zhornitsky *et al.*, 2015; Bergvall *et al.*, 2014; Salter *et al.*, 2014; Agashivala *et al.*, 2013; Fernández *et al.*, 2012; Devonshire *et al.*, 2011; Fraser, Hadjimichael and Vollmer, 2003; Fraser, Hadjimichael and Vollmer, 2001); all were observational as opposed to experimental and there were no qualitative studies found, though a minority of surveys did include free response options (Wicks *et al.*, 2016; Hupperts *et al.*, 2014; Devonshire *et al.*, 2011; Treadaway *et al.*, 2009). Thirteen were cross-sectional in design (Jongen, Wim and Boringa, 2016; Wicks *et al.*, 2016; Lulu *et al.*, 2014; Salter *et al.*, 2014;

¹ The categorisations used in these two data points were specifically labelled by me to align with the COM-B sub-components shown in Figure 1 and to map to the BCT taxonomy definitions, they were not necessarily explicitly stated this way in the paper itself

Koudriavtseva *et al.*, 2012; Lugaresi *et al.*, 2012; de Seze, Borgel and Brudon, 2012; Fernández *et al.*, 2012; Devonshire *et al.*, 2011; Daugherty *et al.*, 2005; Fraser, Hadjimichael and Vollmer, 2003; Fraser, Hadjimichael and Vollmer, 2001; Mohr *et al.*, 2001), with the other twenty being cohort studies (Fernández *et al.*, 2016; Turner *et al.*, 2016; Warrender-Sparkes *et al.*, 2016; He *et al.*, 2015; Zhornitsky *et al.*, 2015; Bergvall *et al.*, 2014; Glanz *et al.*, 2014; Hupperts *et al.*, 2014; Agashivala *et al.*, 2013; Beer *et al.*, 2011; Hancock, Bruce and Lynch, 2011; Bruce *et al.*, 2010; Treadaway *et al.*, 2009; Turner *et al.*, 2009; Siegel, Turner and Haselkorn, 2008; Tremlett *et al.*, 2008; Turner *et al.*, 2007; Rio *et al.*, 2005; Berger, Hudmon and Liang, 2004; Fraser *et al.*, 2004).

In twenty-five studies, data on potential factors relating to adherence were gathered through surveys or structured interviews (Jongen, Wim and Boringa, 2016; Turner *et al.*, 2016; Wicks *et al.*, 2016; Glanz *et al.*, 2014; Hupperts *et al.*, 2014; Lulu *et al.*, 2014; Salter *et al.*, 2014; de Seze, Borgel and Brudon, 2012; Fernández *et al.*, 2012; Koudriavtseva *et al.*, 2012; Lugaresi *et al.*, 2012; Beer *et al.*, 2011; Devonshire *et al.*, 2011; Bruce *et al.*, 2010; Treadaway *et al.*, 2009; Turner *et al.*, 2009; Siegel, Turner and Haselkorn, 2008; Tremlett *et al.*, 2008; Turner *et al.*, 2007; Daugherty *et al.*, 2005; Berger, Hudmon and Liang, 2004; Fraser *et al.*, 2004; Fraser, Hadjimichael and Vollmer, 2003; Mohr *et al.*, 2001; Fraser, Hadjimichael and Vollmer, 2001), whilst eleven used prescriptions or clinical database data (Warrender-Sparkes *et al.*, 2016; He *et al.*, 2015; Zhornitsky *et al.*, 2015; Bergvall *et al.*, 2014; Fernández *et al.*, 2012; Hancock, Bruce and Lynch, 2011; Tremlett *et al.*, 2008; Rio *et al.*, 2005; Fraser, Hadjimichael and Vollmer, 2003; Fraser, Hadjimichael and Vollmer, 2001; Mohr *et al.*, 2001). Five

studies combined these methods (Fernández *et al.*, 2012; Hancock, Bruce and Lynch, 2011; Fraser, Hadjimichael and Vollmer, 2003; Fraser, Hadjimichael and Vollmer, 2001; Mohr *et al.*, 2001).

Adherence outcome data was collected via self-report in twenty-one studies (Jongen, Wim and Boringa, 2016; Turner *et al.*, 2016; Wicks *et al.*, 2016; Glanz *et al.*, 2014; Hupperts *et al.*, 2014; Lulu *et al.*, 2014; Salter *et al.*, 2014; de Seze, Borgel and Brudon, 2012; Fernández *et al.*, 2012; Koudriavtseva *et al.*, 2012; Lugaresi *et al.*, 2012; Beer *et al.*, 2011; Devonshire *et al.*, 2011; Bruce *et al.*, 2010; Treadaway *et al.*, 2009; Turner *et al.*, 2009; Tremlett *et al.*, 2008; Turner *et al.*, 2007; Daugherty *et al.*, 2005; Berger, Hudmon and Liang, 2004; Fraser *et al.*, 2004; Fraser, Hadjimichael and Vollmer, 2003; Fraser, Hadjimichael and Vollmer, 2001; Mohr *et al.*, 2001), prescriptions or clinical records in eleven studies (Warrender-Sparkes *et al.*, 2016; He *et al.*, 2015; Zhornitsky *et al.*, 2015; Bergvall *et al.*, 2014; Agashivala *et al.*, 2013; Fernández *et al.*, 2012; Hancock, Bruce and Lynch, 2011; Tremlett *et al.*, 2008; Rio *et al.*, 2005; Fraser, Hadjimichael and Vollmer, 2003; Mohr *et al.*, 2001) and via electronic monitoring in three (Fernández *et al.*, 2016; Hancock, Bruce and Lynch, 2011; Bruce *et al.*, 2010). Six studies featured a combination of collection methods (Fernández *et al.*, 2012; Hancock, Bruce and Lynch, 2011; Bruce *et al.*, 2010; Fraser, Hadjimichael and Vollmer, 2003; Fraser, Hadjimichael and Vollmer, 2001; Mohr *et al.*, 2001). Twenty studies looked at treatment discontinuation or switching as an outcome (Fernández *et al.*, 2016; Jongen, Wim and Boringa, 2016; Warrender-Sparkes *et al.*, 2016; Wicks *et al.*, 2016; He *et al.*, 2015; Zhornitsky *et al.*, 2015; Bergvall *et al.*, 2014; Salter *et al.*, 2014; Agashivala *et al.*, 2013; de Seze, Borgel and Brudon, 2012; Koudriavtseva *et al.*, 2012; Beer *et al.*, 2011; Tremlett *et al.*,

2008; Daugherty *et al.*, 2005; Rio *et al.*, 2005; Berger, Hudmon and Liang, 2004; Fraser *et al.*, 2004; Fraser, Hadjimichael and Vollmer, 2003; Fraser, Hadjimichael and Vollmer, 2001; Mohr *et al.*, 2001), nineteen focussed on dosing adherence (Fernández *et al.*, 2016; Jongen, Wim and Boringa, 2016; Turner *et al.*, 2016; Bergvall *et al.*, 2014; Glanz *et al.*, 2014; Hupperts *et al.*, 2014; Lulu *et al.*, 2014; Agashivala *et al.*, 2013; de Seze, Borgel and Brudon, 2012; Fernández *et al.*, 2012; Koudriavtseva *et al.*, 2012; Lugaresi *et al.*, 2012; Devonshire *et al.*, 2011; Hancock, Bruce and Lynch, 2011; Bruce *et al.*, 2010; Treadaway *et al.*, 2009; Turner *et al.*, 2009; Siegel, Turner and Haselkorn, 2008; Turner *et al.*, 2007) and six looked at both together (Fernández *et al.*, 2016; Jongen, Wim and Boringa, 2016; Bergvall *et al.*, 2014; Agashivala *et al.*, 2013; de Seze, Borgel and Brudon, 2012; Koudriavtseva *et al.*, 2012). One study (Tremlett *et al.*, 2008) explored the relationship between dosing adherence and persistence.

There were a range of measures used to determine dosing adherence; including Medicines Possession Ratio (MPR) (n=11) (Fernández *et al.*, 2016; Jongen, Wim and Boringa, 2016; Turner *et al.*, 2016; Bergvall *et al.*, 2014; Lulu *et al.*, 2014; Agashivala *et al.*, 2013; Lugaresi *et al.*, 2012; Devonshire *et al.*, 2011; Turner *et al.*, 2009; Siegel, Turner and Haselkorn, 2008; Turner *et al.*, 2007), Proportion of Days Covered (PDC) (n=2) (Bergvall *et al.*, 2014; Agashivala *et al.*, 2013), percentage of doses missed (n=4) (Glanz *et al.*, 2014; Hupperts *et al.*, 2014; Hancock, Bruce and Lynch, 2011; Bruce *et al.*, 2010) and number of doses missed (n=4) (de Seze, Borgel and Brudon, 2012; Fernández *et al.*, 2012; Koudriavtseva *et al.*, 2012; Treadaway *et al.*, 2009) Two studies looked at both MPR and PDC (Bergvall *et al.*, 2014; Agashivala *et al.*, 2013). Of the eleven studies that reported MPR, nine used a

cut-off rate of <80% to define non-adherence (Fernández *et al.*, 2016; Turner *et al.*, 2016; Bergvall *et al.*, 2014; Lulu *et al.*, 2014; Agashivala *et al.*, 2013; Lugaresi *et al.*, 2012; Turner *et al.*, 2009; Siegel, Turner and Haselkorn, 2008; Turner *et al.*, 2007), one study (Jongen, Wim and Boringa, 2016) defined it as <95% and another single study defined it as <100% (Devonshire *et al.*, 2011).

Factors impacting adherence

A summary of factors influencing adherence is given below and, due to the volume of factors which appear only once, this section has been limited to describing only those which appeared in more than one study as significantly correlated with non-adherence or elicited directly from patients through survey responses. Whilst this review is not about relative impact per se, its purpose is to determine the extent to which the two research areas of drivers of nonadherence and adherence interventions complement each other. The large number of single factors meant that there was a risk of the research question being unduly biased towards the negative (e.g. little cohesion) and therefore it was felt that some prioritisation was required.

To further aid grouping and classification, I give 'equivalent' names in the descriptions below. For example, adverse events were classified with side effects and cognitive benefit classified with perceived treatment efficacy. However, for transparency, original descriptions from the studies remain in Table 3. Where applicable the direction of the relationship between a factor and non-adherence is positive unless otherwise stated. Category factors are labelled with the influencing component (e.g. Gender [female]).

Overall, twenty-nine different factors, which appeared more than once, were identified across the studies and have been clustered into the following five

groups of variables: clinical, demographic, opportunity, psychosocial and treatment.

They were not mapped to COM-B at this stage to allow for the findings to be initially presented in categories that were salient with the way research to date has been described.

Clinical variables

Relapse features were found to be the most prevalent clinical factor, including shorter length of time since last relapse (Warrender-Sparkes *et al.*, 2016; Hancock, Bruce and Lynch, 2011; Tremlett *et al.*, 2008), the number of relapses whilst on treatment (Lulu *et al.*, 2014; Treadaway *et al.*, 2009) and total number of relapses across the study period, though this was positively correlated in one (Bergvall *et al.*, 2014) and negatively correlated in another (Fernández *et al.*, 2016). Two studies found a significant impact of greater levels of disability (Zhornitsky *et al.*, 2015; Rio *et al.*, 2005), whilst one found that a lower level of disability was predictive on non-adherence (Berger, Hudmon & Liang *et al.*, 2004). Three reported longer duration of disease (Devonshire *et al.*, 2011; Treadaway *et al.*, 2009; Turner *et al.*, 2007). Two studies found a relationship between the presence of comorbidities and non-adherence (Fernández *et al.*, 2012; Treadaway *et al.*, 2009).

Demographic variables

Age related variables were the most prolific in this category with older age related to non-adherence in two studies (Bergvall *et al.*, 2014; Fernández *et al.*, 2012) and younger age in another two (de Seze, Borgel and Brudon, 2012, Turner *et al.*, 2007). Younger age at treatment initiation was a factor in two studies (Warrender-Sparkes *et al.*, 2016; Zhornitsky *et al.*, 2015). Five

studies found a significant impact of gender, three demonstrated that non-adherence was correlated with being female (Warrender-Sparkes *et al.*, 2016; Bergvall *et al.*, 2014; Beer *et al.*, 2011) and two with being male (Jongen, Wim and Boringa, 2016; Devonshire *et al.*, 2011). A lower level of education was found to be significant in one study (Tremlett *et al.*, 2008), and higher level of education in two others (Devonshire *et al.*, 2011; Berger, Hudmon & Liang *et al.*, 2004).

Opportunity variables

Three studies demonstrated that cost related issues (e.g. less co-pay, higher value drugs) were a factor in non-adherence (Bergvall *et al.*, 2014; Treadaway *et al.*, 2009; Daugherty *et al.*, 2005). A negative impact of travelling was proposed in two studies, whereby people found it more difficult to be adherent when travelling (de Seze, Borgel and Brudon, 2012; Treadaway *et al.*, 2009). Physician support of treatment was found to have a positive impact on adherence in two studies (Fraser, Hadjimichael and Vollmer, 2003; Fraser, Hadjimichael and Vollmer, 2001). Three studies reported patients having a lack of ongoing support with injections as contributing to non-adherence (Devonshire *et al.*, 2011; Treadaway *et al.*, 2009; Mohr *et al.*, 2001). Similarly, a lack of caregiver support and / or congruence in treatment beliefs was evident from three studies (Salter *et al.*, 2014; Devonshire *et al.*, 2011; Fraser, Hadjimichael and Vollmer, 2003).

Psychosocial variables

Forgetting was stated as a reason for non-adherence in seven studies (Hupperts *et al.*, 2014; Lulu *et al.*, 2014; de Seze, Borgel and Brudon, 2012; Fernández *et al.*, 2012; Lugaresi *et al.*, 2012; Devonshire *et al.*, 2011;

Treadaway *et al.*, 2009). Lower self-efficacy was correlated with non-adherence in four (Fraser *et al.*, 2004; Fraser, Hadjimichael and Vollmer, 2003; Fraser, Hadjimichael and Vollmer, 2001; Mohr *et al.*, 2001). The presence of an emotional disorder or higher emotional impact was identified in two studies (Bruce *et al.*, 2010; Treadaway *et al.*, 2009) and a lower degree of hope was a factor in two studies (Treadaway *et al.*, 2009; Fraser, Hadjimichael and Vollmer, 2001). Perception of quality of life was positively correlated with adherence in two papers (Devonshire *et al.*, 2011; Treadaway *et al.*, 2009).

Treatment variables

Treatment variables were the most prolific in these studies. The two most prominent factors were the experience of side effects (n=12) (Fernández *et al.*, 2016; Jongen, Wim and Boringa, 2016; Warrender-Sparkes *et al.*, 2016; Wicks *et al.*, 2016; Hupperts *et al.*, 2014; de Seze, Borgel and Brudon, 2012; Fernández *et al.*, 2012; Lugaresi *et al.*, 2012; Beer *et al.*, 2011; Devonshire *et al.*, 2011; Treadaway *et al.*, 2009; Daugherty *et al.*, 2005) and perceptions of treatment efficacy (n=10) (Fernández *et al.*, 2016; Jongen, Wim and Boringa, 2016; Warrender-Sparkes *et al.*, 2016; Wicks *et al.*, 2016; Salter *et al.*, 2014; de Seze, Borgel and Brudon, 2012; Koudriavtseva *et al.*, 2012; Beer *et al.*, 2011; Treadaway *et al.*, 2009; Daugherty *et al.*, 2005), with greater efficacy perceptions linked to greater adherence. Method of treatment administration was a factor in five studies, with injection treatments leading to greater levels of non-adherence when compared to oral formulations (Wicks *et al.*, 2016; Zhornitsky *et al.*, 2015; Bergvall *et al.*, 2014; Agashivala *et al.*, 2013; Beer *et al.*, 2011). Similarly, a number of injection related factors were also found to impact adherence. They included injection anxiety (Hupperts *et al.*, 2014;

Devonshire *et al.*, 2011; Treadaway *et al.*, 2009; Turner *et al.*, 2009; Mohr *et al.*, 2001), injection fatigue (Wicks *et al.*, 2016; de Seze, Borgel and Brudon, 2012; Fernández *et al.*, 2012; Beer *et al.*, 2011; Devonshire *et al.*, 2011; Treadaway *et al.*, 2009) and pain at the site of injection (Hupperts *et al.*, 2014; Fernández *et al.*, 2012; Lugaresi *et al.*, 2012; Devonshire *et al.*, 2011). Four studies found an impact of dosing frequency (Glanz *et al.*, 2014; Devonshire *et al.*, 2011; Treadaway *et al.*, 2009; Tremlett *et al.*, 2008) with more doses increasing chances of non-adherence and prior treatment status was significantly related to non-adherence in three; prior use of a different treatment in two (Bergvall *et al.*, 2014; Treadaway *et al.*, 2009) and prior use of the same treatment in the other (Fraser, Hadjimichael and Vollmer, 2001). Treatment concerns were cited in two studies (Wicks *et al.*, 2016; Berger, Hudmon and Liang, 2004), as was a longer duration on treatment (Koudriavtseva *et al.*, 2012; Devonshire *et al.*, 2011).

Table 3: Overview of adherence factor studies, including study design and significant outcomes

#	Author; year; country	Study type; collection methods; sample size; type and definition of adherence measured	Significant or patient elicited factors impacting non-adherence
#1	(Agashivala <i>et al.</i> , 2013) USA	Retrospective, observational, cohort; prescription database; n=1891; persistence => 60 day gap, adherence MPR / PDC	Significant factors: Treatment <ul style="list-style-type: none"> • Method of administration (injection)
#2	(Beer <i>et al.</i> , 2011) Switzerland	Prospective, observational; cohort; skin examination and self-report; n=412, treatment discontinuation or switch at 12-month follow-up	Patient elicited factors: Treatment <ul style="list-style-type: none"> • Perceived efficacy* • Side effects (experienced) • Injection fatigue Clinical <ul style="list-style-type: none"> • Flu like symptoms • Abnormal liver function Significant factors: Demographic <ul style="list-style-type: none"> • Gender (female) Treatment <ul style="list-style-type: none"> • Method of administration (injection)
#3	(Bergvall <i>et al.</i> , 2014) USA	Retrospective, observational, cohort; prescription database; n=3750; persistence => 60 day gap, MPR / PDC <80%	Significant factors: Clinical <ul style="list-style-type: none"> • Greater no. of relapses • Headache • Numbness Demographic <ul style="list-style-type: none"> • Age • Gender (female) Opportunity <ul style="list-style-type: none"> • Higher cost Treatment <ul style="list-style-type: none"> • Prior use of other treatment • Method of administration (injection)
#4	(Bruce <i>et al.</i> , 2010) USA	Prospective, observational, cohort; self-report, MEMS, survey; n=55; <10% of doses missed	Significant factors: Psychosocial <ul style="list-style-type: none"> • Cognition ('comparative reduced capacity' in memory, list recall, list learning) • Emotional disorder (presence of) • Personality (neuroticism, openness, conscientiousness*)
#5	(Lugaresi <i>et al.</i> , 2012) Italy	Prospective, observational, crosssectional; survey; n=109; MPR =>80%	Patient elicited factors: Psychosocial <ul style="list-style-type: none"> • Forgetting Treatment <ul style="list-style-type: none"> • Adverse events • Injection site pain • Device problems

#	Author; year; country	Study type; collection methods; sample size; type and definition of adherence measured	Significant or patient elicited factors impacting non-adherence
#6	(He <i>et al.</i> , 2015) Multi-country sample	Retrospective, observational, cohort; registry database; n=527; treatment discontinuation at follow-up (13.1 month median)	No significant findings
#7	(Hupperts <i>et al.</i> , 2014) Multi-country sample	Prospective, observational, cohort; survey; n=251; % of doses taken	<p>Patient elicited factors:</p> <p>Psychosocial</p> <ul style="list-style-type: none"> • Forgetting • Fatigue <p>Treatment</p> <ul style="list-style-type: none"> • Adverse events • Injection site pain • Injection anxiety
#8	(Koudriavtseva <i>et al.</i> , 2012) Italy	Prospective, observational, cross sectional; structured interview; n=97; 'very good' = no doses missed, 'other' = some doses missed, discontinuation >1 month	<p>Significant factors:</p> <p>Opportunity</p> <ul style="list-style-type: none"> • No choice in physician <p>Treatment</p> <ul style="list-style-type: none"> • Perceived efficacy* • Duration
#9	(Lulu <i>et al.</i> , 2014) USA	Prospective, observational, cross sectional; surveys; n=30; MPR=<80	<p>Patient elicited factors:</p> <p>Psychosocial</p> <ul style="list-style-type: none"> • Forgetting • Interferes with activities • Want to forget condition • Do not think it is needed <p>Treatment</p> <ul style="list-style-type: none"> • Injection pain / bruising • Side effects <p>Opportunity</p> <ul style="list-style-type: none"> • Cost • Ran out of medication <p>Significant factors:</p> <p>Clinical</p> <ul style="list-style-type: none"> • Relapsed when on treatment
#10	(Mohr <i>et al.</i> , 2001) USA	Prospective, observational, cross-sectional; prescription data and psychosocial assessment; n=101; treatment discontinuation	<p>Significant factors:</p> <p>Treatment</p> <ul style="list-style-type: none"> • Injection anxiety <p>Opportunity</p> <ul style="list-style-type: none"> • Injection administrator (<i>other person needed</i>) <p>Psychosocial</p> <ul style="list-style-type: none"> • Self-efficacy*

#	Author; year; country	Study type; collection methods; sample size; type and definition of adherence measured	Significant or patient elicited factors impacting non-adherence
#11	(Salter <i>et al.</i> , 2014) USA	Retrospective, observational, cross-sectional; patient survey; n=308; switching treatment	Patient elicited factors: Treatment <ul style="list-style-type: none"> Perceived efficacy*
#12	(Siegel, Turner and Haselkorn, 2008) USA	Prospective, observational, cohort; self-report; n=54; MPR=>80%	Patient elicited factors: Opportunity <ul style="list-style-type: none"> Supportive qualities of caregiver
#13	(Rio <i>et al.</i> , 2005) Spain	Prospective, observational, cohort; clinical database; n=622; treatment discontinuation	Significant factors: Clinical <ul style="list-style-type: none"> Type of MS (SPMS) Greater disability
#14	(Treadaway <i>et al.</i> , 2009) USA	Prospective, observational, cohort; survey; n=798; missing any injection in a 4-week period	Patient elicited factors: Clinical <ul style="list-style-type: none"> Headache Weakness Flu like symptoms Fatigue Comorbidity present Relapse Psychosocial <ul style="list-style-type: none"> Injection anxiety Forgetting Depression Didn't feel like it Treatment <ul style="list-style-type: none"> Perception of efficacy* Injection fatigue Injection pain Skin reactions Inconvenient dosing Opportunity <ul style="list-style-type: none"> Emergency No support with injection Cost Ran out of medication Travelling Pharmacy delivery issues Significant factors: Demographic <ul style="list-style-type: none"> Diagnosis age* Disease duration* Not on first treatment

#	Author; year; country	Study type; collection methods; sample size; type and definition of adherence measured	Significant or patient elicited factors impacting non-adherence
			Psychosocial <ul style="list-style-type: none"> • Reduced cognitive function • Role limitations (physical) • Emotional problems • Emotional wellbeing* • Depression • Treatment satisfaction* • QoL perceptions* • Hope* • Social function* Clinical <ul style="list-style-type: none"> • Energy • Physical composite • Mental composite • Change in health • Pain
#15	(Wicks <i>et al.</i> , 2016) USA	Prospective, observational, cross sectional; survey; n=281; treatment discontinuation or switch	Patient elicited factors: Treatment <ul style="list-style-type: none"> • Side effects (experienced) • Oral preference • Struggling to administer / take • Concerns • Lack of efficacy
#16	(Turner <i>et al.</i> , 2009) USA	Prospective, observational, cohort; structured interviews; n=89; MPR =>80%	Significant factors: Treatment <ul style="list-style-type: none"> • Injection anxiet
#17	(Turner <i>et al.</i> , 2007) USA	Prospective, observational, cohort; structured interviews; n=89; MPR =>80%	Significant factors: Demographic <ul style="list-style-type: none"> • Age* Clinical <ul style="list-style-type: none"> • Years since diagnosis Psychosocial <ul style="list-style-type: none"> • HBM Severity • HBM Benefits*
#18	(Tremlett <i>et al.</i> , 2008) Tasmania	Prospective, observational, cohort; survey and clinical assessment; n=97; treatment discontinuation	Significant factors: Demographic <ul style="list-style-type: none"> • Lower education Treatment <ul style="list-style-type: none"> • Prior missed doses • More frequent administration Clinical <ul style="list-style-type: none"> • Time since last relapse* Psychosocial <ul style="list-style-type: none"> • Alcohol consumption

#	Author; year; country	Study type; collection methods; sample size; type and definition of adherence measured	Significant or patient elicited factors impacting non-adherence
#19	(Warrender Sparkes <i>et al.</i> , 2016) Multi-country	Prospective, observational, cohort; clinical database; n=4,111; treatment discontinuation	Significant factors: Demographic <ul style="list-style-type: none"> • Gender (female) • Country (Australian) • Age at start of treatment* Clinical <ul style="list-style-type: none"> • <6 months since last relapse Treatment <ul style="list-style-type: none"> • Adverse events • Tolerance* • Efficacy*
#20	(Turner <i>et al.</i> , 2016) USA	Prospective, observational, cohort; structured interviews; n=89; MPR =>80%	Significant predictors Psychosocial <ul style="list-style-type: none"> • Adherence expectations*
#21	(Fernández <i>et al.</i> , 2012) Spain	Retrospective, observational, cross sectional; self-report, prescription data; n=120; Morisky-Green test, prescriptions dispensed; no of doses missed	Significant predictors Demographic <ul style="list-style-type: none"> • Age Patient elicited reasons Treatment <ul style="list-style-type: none"> • Side effects • Injection site pain Clinical <ul style="list-style-type: none"> • Infection • Comorbidities • Fatigue Psychosocial <ul style="list-style-type: none"> • Forgetting • Social commitments
#22	(Zhornitsky <i>et al.</i> , 2015) Canada	Retrospective, observational, cohort; clinical database; n=1,471; treatment discontinuation	Significant predictors Treatment <ul style="list-style-type: none"> • Type Demographic <ul style="list-style-type: none"> • Age (starting treatment before age 30) Clinical <ul style="list-style-type: none"> • Disability at treatment initiation
#23	(Jongen, Wim and Boringa, 2016) Netherlands	Prospective, observational, crosssectional; survey; n=200; treatment discontinuation and MPR =<95%	Patient elicited factors: System <ul style="list-style-type: none"> • Time with psychological care* • Time with other medical specialists* • Time receiving home care* • Time receiving informal care* Treatment <ul style="list-style-type: none"> • Side effects • Efficacy* Demographic <ul style="list-style-type: none"> • Gender (male)

#	Author; year; country	Study type; collection methods; sample size; type and definition of adherence measured	Significant or patient elicited factors impacting non-adherence
#24	(Hancock, Bruce and Lynch, 2011) USA	Prospective, observational, cohort; clinical records, MEMS, self-report; n=75; % of missed doses	Significant predictors: Clinical <ul style="list-style-type: none"> • Time since last relapse* • Steroid use* • Adherence to medical appointments*
#25	(Glanz <i>et al.</i> , 2014) USA	Prospective, observational cohort; survey; n=226; % of missed doses	Significant predictors: Treatment <ul style="list-style-type: none"> • No. of doses Psychosocial <ul style="list-style-type: none"> • Inconvenience
#26	(Fernández <i>et al.</i> , 2016) Spain	Retrospective, observational, cohort; electronic device; n=258; MPR =<80%; treatment discontinuation	Significant predictors: Treatment <ul style="list-style-type: none"> • Adverse events • Efficacy Clinical <ul style="list-style-type: none"> • No. of relapses*
#27	(Fraser <i>et al.</i> , 2004) USA	Prospective, observational, cohort; survey; n=104; treatment discontinuation	Significant predictors: Psychosocial <ul style="list-style-type: none"> • Self-efficacy*
#28	(Fraser, Hadjimichael and Vollmer, 2003) USA	Retrospective, observational, cross-sectional; survey and registry; n= 199; treatment discontinuation	Significant predictors: Psychosocial <ul style="list-style-type: none"> • Self-efficacy* • Less physician support of treatment • Less spousal support of treatment
#29	(Fraser, Hadjimichael and Vollmer, 2001) USA	Retrospective, observational, cross-sectional; survey and registry; n= 341; treatment discontinuation	Significant predictors: Psychosocial <ul style="list-style-type: none"> • Self-efficacy* • Hope* • Less physician support of treatment Treatment <ul style="list-style-type: none"> • Previous use of treatment class

#	Author; year; country	Study type; collection methods; sample size; type and definition of adherence measured	Significant or patient elicited factors impacting non-adherence
#30	(Devonshire <i>et al.</i> , 2011) Multi country	Retrospective, observational, crosssectional; survey; n=2,566; MPR<100%	<p>Significant predictors:</p> <p>Treatment</p> <ul style="list-style-type: none"> • Dose frequency • Time on treatment • Difficulty of injection <p>Clinical</p> <ul style="list-style-type: none"> • Disease duration • Neuropsychological impairment <p>Opportunity</p> <ul style="list-style-type: none"> • Physician not discuss adherence at initiation • Not treated at a dedicated MS centre • Frequency of neurologist appointments* • Less support from spouse / partner <p>Demographic</p> <ul style="list-style-type: none"> • Gender (male) • Education level <p>Psychosocial</p> <ul style="list-style-type: none"> • Satisfaction with treatment* • Quality of life* <p>Patient elicited factors:(min. 10% of ppt)</p> <p>Treatment</p> <ul style="list-style-type: none"> • Injection fatigue • Injection site pain • Injection anxiety • Side effects <p>Psychosocial</p> <ul style="list-style-type: none"> • Treatment necessity • Forgetting <p>Opportunity</p> <ul style="list-style-type: none"> • No-one to support with injections <p>Clinical</p> <ul style="list-style-type: none"> • Symptoms

#	Author; year; country	Study type; collection methods; sample size; type and definition of adherence measured	Significant or patient elicited factors impacting non-adherence
#31	(de Seze, Borgel and Brudon, 2012) France	Prospective, observational, crosssectional; survey; n = 202; treatment discontinuation, switch, missing doses	Significant predictors: Demographic <ul style="list-style-type: none"> • Age* Psychosocial <ul style="list-style-type: none"> • Disease understanding* • Forgetting • Wanting to forget illness • Perceived efficacy* Treatment <ul style="list-style-type: none"> • Injection fatigue • Side effects Opportunity <ul style="list-style-type: none"> • Travel / Holiday
#32	(Berger, Hudmon and Liang, 2004) USA	Prospective, observational, cohort; interview and survey; n=531; treatment discontinuation	Significant predictors: Demographic <ul style="list-style-type: none"> • Level of education • Level of disability* Treatment <ul style="list-style-type: none"> • Perceived pros of treatment* • Perceived cons of treatment
#33	(Daugherty <i>et al.</i> , 2005) USA	Prospective, observational, crosssectional; survey; n=108; treatment discontinuation	Significant predictors: Treatment <ul style="list-style-type: none"> • Side effects • Perceptions of efficacy* Opportunity <ul style="list-style-type: none"> • Cost

*Signifies a negative correlation or association

Comparison of findings to the COM-B model of adherence

Firstly, where possible, the factors identified from the scoping review (that appeared more than once) were mapped against and categorised as per the COM-B model for adherence (Jackson *et al.*, 2014). The aim of this, in line with the original research objectives, was to help to rationalise (further) the

disparate descriptions of adherence drivers / barriers against an evidence-based adherence model. Fourteen factors (48%) mapped directly; cognitive function (forgetting) beliefs about treatment (concerns [includes side effects], efficacy), self-efficacy, mood state / disorder, cost, caregiver support (general and specific help with injections), dosing, packaging considerations of medicine (oral preference, injection fatigue, injection anxiety, injection site pain), HCP relationship / communication (physician support of treatment).

Fourteen factors (52%) remained that could not be mapped directly; clinical factors were, relapse features (time since last relapse, number of relapses on treatment, number of relapses during study timeframe), increased disability, time since diagnosis and comorbidities. Demographic factors included age, gender and education level. Psychosocial elements that couldn't be directly mapped were hope and quality of life; patients in two studies cited travelling as an adherence barrier. Treatment variables included prior treatment status, both being on a different treatment and the same treatment previously as well as duration on treatment.

From the original COM-B model for adherence, ten factors did not appear in the rationalised list from the literature: comprehension of disease / treatment, executive functioning, physical capability to adapt to lifestyle changes, dexterity, perceptions of illness, outcome expectancies, stimuli / cues for action, access to treatment, stigma and religious / cultural beliefs.

Table 4 shows how the findings from the literature review did and did not match the COM-B model of adherence as proposed by Jackson and colleagues (2014).

Of those factors from the review that could not be mapped directly, it was possible to align four of them to the COM-B categories, based on the category descriptions, namely: increased disability within physical capability, hope and quality of life within reflective motivation and travelling within physical opportunity. This alignment is shown in Table 5.

From these insights it was possible to propose a revised COM-B model specifically for adherence to DMTs in MS, shown in Figure 5. This model was used as the basis for the second part of the review; MS adherence factors successfully modified through intervention.

Table 4 – Comparison of findings from the factors review to the COM-b model of adherence

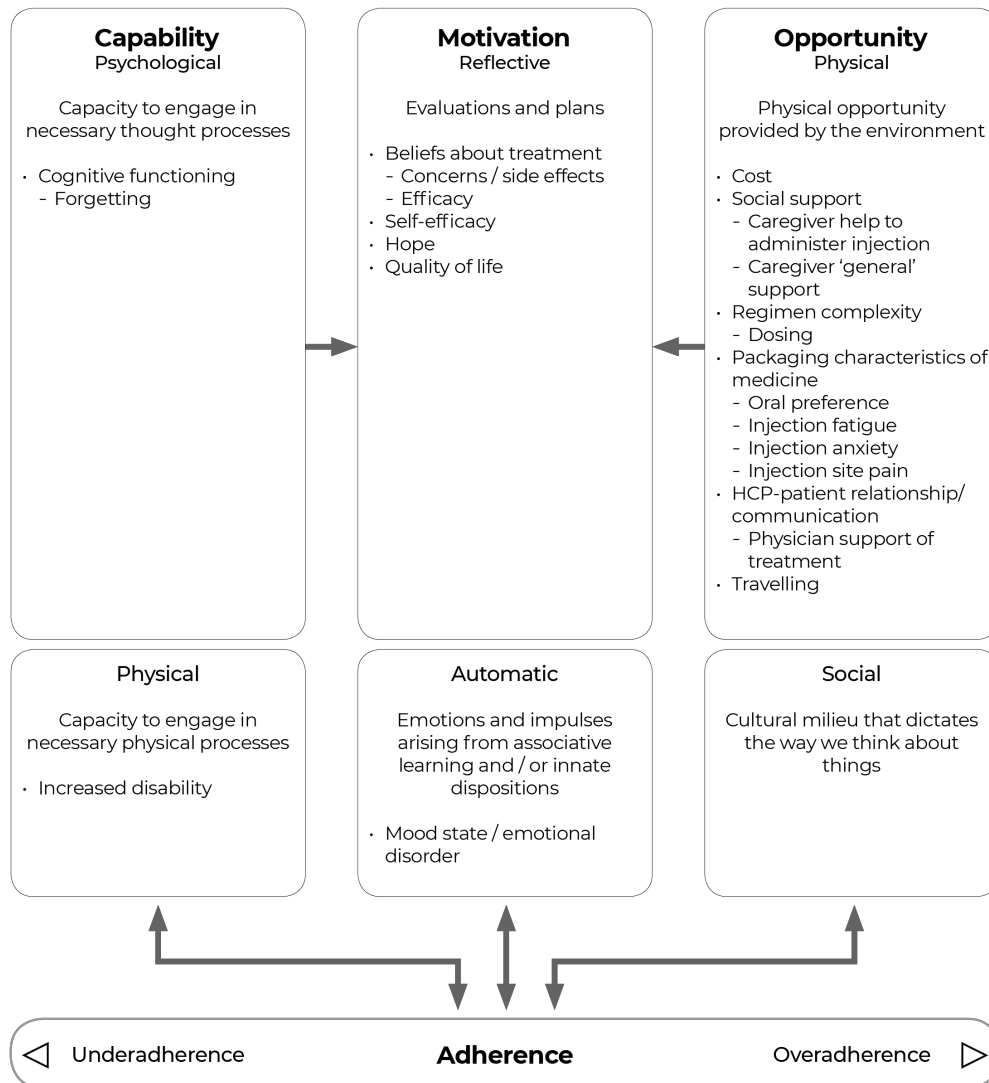
Category	Factors from the original model identified* in the review	Factors from the original model not identified * in the review
Capability (psychological)	Cognitive functioning <ul style="list-style-type: none"> • Forgetting 	Comprehension of disease and treatment Executive function (e.g. capacity to plan)
Capability (physical)	n/a	Physical capability to adapt to lifestyle changes Dexterity
Motivation (reflective)	Beliefs about treatment <ul style="list-style-type: none"> • Concerns / side effects • Efficacy Self-efficacy	Perceptions of illness Outcome expectancies
Motivation (automatic)	Mood state / emotional disorder	Stimuli or cues for action
Opportunity (physical)	Cost Social support <ul style="list-style-type: none"> • Caregiver help to administer injection • Caregiver 'general' support Regimen complexity <ul style="list-style-type: none"> • Dosing Packaging characteristics of medicine <ul style="list-style-type: none"> • Oral preference • Injection fatigue • Injection anxiety • Injection site pain HCP-patient relationship/communication <ul style="list-style-type: none"> • Physician support of treatment 	Access (e.g. availability of medication)
Opportunity (social)	n/a	Stigma of disease, fear of disclosure Religious / cultural beliefs

**needs to have appeared more than once to 'qualify' as per description above*

Table 5 – Factors from the review that could be mapped to COM-B categories, but do not appear in the original adherence model

Category	Factors identified in the review that were not in the original model which could be mapped to the COM-B categories
Capability (psychological)	n/a
Capability (physical)	Increased disability
Motivation (reflective)	Hope Quality of life
Motivation (automatic)	n/a
Opportunity (physical)	Travelling
Opportunity (social)	n/a

Figure 5 – Revised COM-B for adherence to DMTs in people with MS



Review 2: MS Adherence factors successfully modified through intervention

Overview

The total sample size across the studies was 750 (range 12-367; mean 187.5). Of the four studies that met the inclusion criteria, three were RCTs (Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005; Mohr *et al.*, 2000) and one was a prospective, observational, cohort study (Zetl *et al.*, 2016). All were single country studies from Germany (Zetl *et al.*, 2016) and the USA (Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005; Mohr *et al.*, 2000). An overview of these studies is shown in Table 6

Table 6: Overview of successful intervention studies, including study design, factors targeted, behaviour change techniques applied and the significant outcomes

#	Author; year; country	Study type; collection methods; sample size; type and definition of adherence measured; intervention approach	Adherence Factors targeted (identified in part 1 of the review)	BCTs applied	Significant outcomes
#1	(Mohr <i>et al.</i> , 2000); USA	RCT, Telephone survey and prescription data; n= 32; persistence at 4 months; Weekly, 50-minute telephone Cognitive Behavioural Therapy approach, delivered over 8 weeks.	Mood state / emotional disorder	Goal setting (behaviour and outcome) Discrepancy between current behaviour and goal Action planning Review behavioural goals Framing / reframing Self-monitoring of behaviour Prompts/cues Social support (unspecified)	Post intervention depression scores lower in treatment group compared to usual care ($p = .02$); depression scores decreased postintervention in treatment group ($p = .0004$) but not in usual care ($p = .69$). Significant relationship between

#	Author; year; country	Study type; collection methods; sample size; type and definition of adherence measured; intervention approach	Adherence Factors targeted (identified in part 1 of the review)	BCTs applied	Significant outcomes
					intervention and persistence ($p = .03$).
#2	(Berger, Liang and Hudmon, 2005); USA	RCT; telephone and web survey; n=367; persistence at 3 months; Transtheoretical Model of Change and motivational interviewing, delivered by telephone, using a software algorithm, at fortnightly or 4weekly intervals for 3 months; educational leaflets	Beliefs about treatment Efficacy Concerns / side effects Self-efficacy Packaging characteristics of medicine Injection site pain	Instruction on how to perform the behaviour Information about health consequences Social support (unspecified) Pros and Cons Framing/reframing	Positive impact of intervention on model stage ($p = <.01$) Perceived importance of treatment (necessity) significantly higher in intervention group ($p = <.05$) Significant relationship between intervention and persistence (1.2% stopped in intervention group compared to 8.7% stopping in standard care; $p = .001$).
#3	(Zetl <i>et al.</i> , 2016); Germany	Prospective, observational, cohort; physician provided data, patient diary data (PDA and Paper); n=339; persistence at 24 months, no. of injections recorded (\Rightarrow 6 missed every six months)	Cognitive function Forgetting Packaging characteristics of medicine Injection site pain	Prompts/cues Self-monitoring of behaviour Instruction on how to perform the behaviour	Significant impact on adherence (no. of injections) of PDA plus reminders compared to PDA without reminders (OR 0.57 [95% CI 0.321-1.018]).

#	Author; year; country	Study type; collection methods; sample size; type and definition of adherence measured; intervention approach	Adherence Factors targeted (identified in part 1 of the review)	BCTs applied	Significant outcomes
		nonadherent); reminders and monitoring, education on treatment administration and adverse events			
#4	(Turner <i>et al.</i> , 2014); USA	RCT; self-report; n=19; no. of injections recorded at 1,3,6 months; motivational interviewing telephone counselling (3 sessions in month 1) and mailed graphic feedback on benefits of treatment, home telehealth monitoring including tailored reminders and positive reinforcement messaging, tracking and telephone followup for nonadherence.	Beliefs about treatment Efficacy Concerns / side effects Self-efficacy Cognitive function Forgetting Packaging characteristics of medicine Injection site pain	Prompts/cues Action planning Problem solving Feedback on behaviour Self-monitoring of behaviour Information about health consequences Salience of consequences Commitment Goal setting (behaviour and outcome) Discrepancy between current behaviour and goal Pros and Cons Instruction on how to perform the behaviour Social support (unspecified)	Significant impact of intervention on no. of injections recorded at 6 months only ($p = <.05$)

Intervention type and delivery

Three of the interventions used telephone counselling, with two of these utilising principles of motivational interviewing (Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005) and one using a Cognitive Behavioural Therapy (CBT) approach (Mohr *et al.*, 2000).

Of these three, two used therapists selected and trained specifically for the study (Turner *et al.*, 2014; Mohr *et al.*, 2000) and one trained existing call centre staff and provided a digital intervention algorithm to guide discussions (Berger, Liang and Hudmon, 2005).

Call times and frequency ranged between the interventions. The CBT based study provided weekly, 50 minute calls over the course of eight weeks (Mohr *et al.*, 2000), one of the MI based interventions delivered calls over three months at either two or four weekly intervals dependent on patient likelihood to adhere (no call length data provided) (Berger, Liang and Hudmon, 2005) and the other MI intervention provided three telephone sessions in month 1 (ranging from 45 – 75 mins each) plus follow-up calls during months two to six in response to non-adherence data being received. These averaged 9.3 minutes in length and across the intervention sample there was an average of four follow-up calls executed (range 1-9) (Turner *et al.*, 2014).

All three telephone counselling interventions also included additional 'paper based' materials. These took the form of a workbook to support the CBT intervention (Mohr *et al.*, 2000), tailored educational leaflets (Berger, Liang and Hudmon, 2005) and tailored graphical information on the benefits of treatment (Turner *et al.*, 2014).

The intervention provided by Turner and colleagues (2014) also provided participants with a home telehealth monitoring system with optional treatment reminders, prompts to record when medicine was taken, positive reinforcement messaging and notifications to the study therapist when injections were not recorded which prompted a follow-up call.

Zettl and colleagues (2016) allowed people to choose between a paper patient diary or personal digital assistant (PDA). Those who selected a PDA were then randomly allocated one with or without an additional reminder function. All diaries included options to record when and where on the body injections were administered plus any skin reactions. The PDA also included a help function with information on self-injection and managing AEs. It is not clear from the intervention description whether any supplementary information was provided in the paper diary (Zettl *et al.*, 2016).

Intervention timeframes varied for each study; eight weeks (Mohr *et al.*, 2000), three months (Berger, Liang and Hudmon, 2005), six months (Turner *et al.*, 2014) and two years (Zettl *et al.*, 2016).

Behaviour change theories and models

Two interventions (Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005), were delivered using principles of Motivational Interviewing which has been defined as a 'counselling style' (Rollnick and Miller, 1995) but it is proposed to be effective through theory-based mechanisms of action (see Miller and Rose, 2009 for a discussion on this). Berger and colleagues (2004), also cited the Transtheoretical Model of Change as a core basis for their intervention design. One used cognitive behavioural therapy (Mohr *et al.*, 2000), which again can be classified as an intervention style, but does draw on a theoretical

approach (Clak and Beck, 1999). One cited no theoretical basis for the design (Zettl *et al.*, 2016).

Describing the interventions using components of the Behaviour Change Wheel

As well as utilising the BCW to structure intervention design, its authors also propose that it can be used to evaluate and synthesize evidence from behaviour change interventions (Michie, Atkins and West, 2014). As a key aim of this review is evidence synthesis, the components of the intervention studies have been described using policy categories, intervention functions and behaviour change techniques, based on my interpretation of the intervention description, utilising guidelines outlined in (Michie, Atkins and West, 2014). How these intervention elements map to factors identified in the COM-B model for adherence to DMTs in MS and alignment to recommended links between components, functions and techniques are explored in the integrated findings section.

Policy categories

As all of these were short-term interventions designed for the purposes of research, the primary policy category applicable to all studies was Service Provision as each one delivered services / support over and above standard care as opposed to implementing a comprehensive 'new' model of care.

Additionally, all studies created and shared Guidelines to help facilitate the delivery of the intervention as per the study protocol. Finally, Communication was a key component of each of the interventions, including telephone, print and electronic information and support.

Intervention functions and Behaviour Change Techniques applied

Across all the studies, a total of five intervention functions were applied; Education, Enablement, Environmental Restructuring, Persuasion and Training. Sixteen BCTs were identified through a review of the intervention descriptions and are listed in Table 7 including their relevant taxonomy categories and codes and the functions they were aligned to in these studies.

Table 7: BCTs and their relevant intervention functions utilised in successful behaviour change interventions for people with MS

BCT Category	BCTs	Intervention functions	Studies
(1) Goals and planning	1.1 Goal setting (behaviour) 1.2 Problem solving 1.3 Goal setting (outcome) 1.4 Action Planning 1.5 Reviewing behavioural goals 1.6 Discrepancy between current behaviour and goals 1.9 Commitment	Enablement	Turner <i>et al.</i> , 2014; Mohr <i>et al.</i> , 2000;
(2) Feedback and monitoring	2.2 Feedback on behaviour 2.3. Self-monitoring of behaviour	Education Enablement Persuasion	Zetl <i>et al.</i> , 2016; Turner <i>et al.</i> , 2014;

		Training	Mohr <i>et al.</i> , 2000
(3) Social support	3.1 Social support (unspecified)	Enablement Persuasion	Turner <i>et al.</i> , 2014; Berger, Liang and Hudmon, 2005; Mohr <i>et al.</i> , 2000
(4) Shaping knowledge	4.1 Instruction on how to perform the behaviour	Training	Zetzl <i>et al.</i> , 2016; Turner <i>et al.</i> , 2014; Berger, Liang and Hudmon, 2005;
(5) Natural consequences	5.1. Information about health consequences 5.2 Salience of consequences	Education Persuasion	Turner <i>et al.</i> , 2014; Berger, Liang and Hudmon, 2005
(7) Associations	7. 1 Prompts / cues	Education Environmental Restructuring	Zetzl <i>et al.</i> , 2016; Turner <i>et al.</i> , 2014; Mohr <i>et al.</i> , 2000
(9) Comparison of outcomes	9.2 Pros and Cons	Enablement	Berger, Liang and Hudmon, 2005
(13) Identity	13.2 Framing / reframing	Enablement	Berger, Liang and Hudmon, 2005; Mohr <i>et al.</i> , 2000

Goals and planning

Goals and planning oriented BCTs were used in two interventions, including goal setting (behaviour and outcome) (Turner *et al.*, 2014; Mohr *et al.*, 2000), reviewing behavioural goals (Mohr *et al.*, 2000), action planning (Turner *et al.*, 2014; Mohr *et al.*, 2000), problem solving (Turner *et al.*, 2014) helping people identify discrepancy between current behaviour and goal (Turner *et al.*, 2014; Mohr *et al.*, 2000) and commitment (Turner *et al.* 2014). In the context of these studies, goals and planning techniques aligned primarily with the intervention function of Enablement.

Associations

Three interventions used prompts/cues, (Zetzl *et al.*, 2016; Turner *et al.*, 2014 ; Mohr *et al.*, 2000). Two of these studies provided explicit reminders or prompts to take medicine (Zetzl *et al.*, 2016; Turner *et al.*, 2014) which aligns with the intervention function of Environmental Restructuring. Mohr and colleagues used prompts/cues in a more educational way through the provision of patient workbooks to facilitate homework between telephone sessions, therefore aligning more closely to the Education function.

Feedback and monitoring

Self-monitoring of behaviour was applied in three interventions (Zetzl *et al.*, 2016; Turner *et al.*, 2014; Mohr *et al.*, 2000). Feedback on behaviour was a feature of one intervention (Turner *et al.*, 2014). Self-monitoring and feedback techniques align to a number of functions according to the published guidance (Michie, Atkins and West, 2014). For Mohr and colleagues (2000) self-monitoring was a tool to enable better understanding of cognitive behaviours (e.g. thought monitoring) and activity levels for those people receiving support with fatigue. To this end the key intervention functions appear to be Education, Training and Enablement. The use of a PDA / paper diary in the study by Zetzl and colleagues (2016) facilitated self-monitoring of adherence and any adverse events, plus a help function / direction on how to reduce and manage AEs. In this context the most aligned intervention functions are Training and Education. In their MI / home monitoring study, Turner and colleagues (2014) prompted self-monitoring to identify potential non-adherence and to adapt the intervention accordingly. They also explored with patients any incongruence between their adherence behaviours and their

desired health outcomes, suggesting that Persuasion was the key intervention function.

Natural consequences

Two of the study interventions included BCTs from the natural consequences category. These were information about health consequences (Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005) which maps to the Education function and salience of consequences (Turner *et al.*, 2014) which maps to the function of Persuasion.

Shaping knowledge

Three studies included the BCT, instruction on how to perform the behaviour (Zettl *et al.*, 2016; Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005), aligned with the intervention function of Training.

Identity

Two studies utilised framing/ reframing techniques, drawn from cognitive behavioural therapy (Berger, Liang and Hudmon, 2005; Mohr *et al.*, 2000). In the context of these interventions, the technique aligned with the function of Enablement as it was a specific technique to support cognitive behavioural change, therefore “increasing means / reducing barriers to increase capability (beyond education and training)” (Michie *et al.*, 2014, pg. 113).

Comparison of outcomes

Also from principles of cognitive behavioural therapy, supporting people to consider the pros and cons of adherence was featured in one study (Berger, Liang and Hudmon, 2005). As with framing / reframing, the use of this technique was supporting cognitive changes beyond just providing information and therefore sits within the function of Enablement also.

Social support

Social support (unspecified) was a feature of three interventions through the provision of telephone counselling (Turner *et al.*, 2014; Mohr *et al.*, 2000; Berger, Liang and Hudmon, 2005). Turner and colleagues (2014) also encouraged the identification of social support as part of their intervention. In this context, social support fits within the function of Enablement as it aims to increase capability beyond just providing education or training. In addition, the two MI based interventions (Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005) would have, by the nature of MI techniques themselves, also have aligned with the function of Persuasion.

Adherence measures

Two studies measured persistence only (Berger, Liang and Hudmon, 2005; Mohr *et al.*, 2000) one examined dosing adherence only (Turner *et al.*, 2014) and one looked at both persistence and dosing adherence (Zettl *et al.*, 2016).

Persistence endpoints were different in the three relevant studies, 3 months (Berger, Liang and Hudmon, 2005), 6 months (Mohr *et al.*, 2000) and 24 months (Zettl *et al.*, 2016). Dosing adherence was defined as total no. of injections recorded in both studies (Zettl *et al.*, 2016; Turner *et al.*, 2014).

Adherence outcome data was collected via self-report in three studies (Zettl *et al.*, 2016; Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005) and prescription data in one (Mohr *et al.*, 2000). The self-report measures used were an adapted single item question asking how many doses missed in the previous month asked via telephone survey (Turner *et al.*, 2014), single item on persistency at three months asked via telephone survey (Berger, Liang and Hudmon, 2005) and reporting treatment continuation and missed doses to

physician during study visits as well as data recorded on the PDA (Zetzl *et al.*, 2016).

Adherence outcomes

The 8-week CBT based intervention had a significant impact on 4-month persistence rates compared to standard care (2 discontinued compared to 9; $p = .03$) (Mohr *et al.*, 2000).

The MI based interventions had a significant impact on both persistence at three months (1.2% of people stopped in the intervention group compared to 8.7% stopping in the standard care; $p = .001$) (Berger, Liang and Hudmon, 2005) and total number of injections recorded at 6 months ($M [SD] = 1.3 [2.1]$ vs $8.2 [12.3]$ past month missed doses; $p < .05$) (Turner *et al.*, 2014).

The PDA intervention demonstrated an impact on number of injections for those who had the additional reminder function, with a mean of 24.5 more injections over 24 months compared to PDA use with no reminder. Comparison data were not available for the paper diary and there was no significant impact on persistence (Zetzl *et al.*, 2016).

Other outcomes

The CBT based intervention demonstrated significantly improved depression scores, as measured by the POMS Depression – Dejection scale (McNair, Lorr & Droppleman, 1981). Post intervention depression scores were lower in the intervention group compared to usual care ($p = .02$), in addition, there was a significant reduction in pre-post intervention depression scores in the intervention group ($p = .0004$) but not in the usual care group ($p = .69$) (Mohr *et al.*, 2000).

One of the MI based interventions (Berger, Liang and Hudmon, 2005), demonstrated a significant, positive impact on patient 'stage of readiness' to discontinue treatment ($p = <.01$) and perceived importance of treatment (measured by response to a single item question) was significantly higher in the intervention group compared to standard care ($p = <.05$). In the discussion section, Berger and colleagues (2005) reported that there was a significant, positive impact on self-efficacy, but the data was not presented in the results section to support this finding and was therefore omitted from Table 6.

Integrated Findings

This section integrates the findings from the two reviews and describes which factors influencing adherence in MS (based on the revised COM-B for adherence in MS, Figure 5) were targeted by the interventions identified in the second review, and how.

Adherence factors targeted by the interventions – COM-B

One study targeted a single factor from the first part of the review (Mohr *et al.*, 2000) whilst the other three targeted multiple factors (Zetl *et al.*, 2016; Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005). In total, five factors from the revised COM-B were addressed, leaving eleven not targeted.

Capability factors

Two capability factors were included in the revised COM-B model and one of these was addressed by two of the interventions reviewed, namely cognitive functioning (forgetting), (Zetl *et al.*, 2016; Turner *et al.*, 2014). Increased disability was not a factor described in the interventions.

Motivational factors

One intervention explicitly and exclusively targeted mood state / emotional disorder (Mohr *et al.*, 2000) and two interventions targeted self-efficacy (Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005). Beliefs about treatment were the focus of two interventions (Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005) with both attempting to address beliefs about efficacy and concerns / side effects. Hope and quality of life from the revised COM-B were not targeted.

Opportunity factors

Opportunity (physical) factors were the most prolific from the review, yet only one was explicitly described as being supported, physical characteristics of medicine (injection site pain). This was a feature of the three of the interventions (Zetzl *et al.*, 2016; Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005). Cost, social support (caregiver general and help with injection), regimen complexity (dosing), HCP-patient relationship/communication (physician support of treatment) and the remaining medicine characteristic factors, oral preference, injection fatigue and injection anxiety were not addressed.

Mapping of Intervention Functions and BCTs to factors

Guidance for use of the BCW includes recommendations for which functions are most appropriate for each of the COM-B categories, referred to as a matrix of links (e.g. Psychological capability maps to the intervention functions of Education, Training and Enablement). In turn, whilst in their guidance Michie and colleagues (2014) acknowledge that, at this time, there are not specific BCT taxonomies for each intervention function, they do provide consensus guidance as to the most appropriate BCTs by intervention function, including prioritisation by frequency of use. The next section describes how the BCTs and factors aligned according to the aims and intervention description of each study and, in turn how whether these alignments matched guidance from Michie and colleagues (2014). Table 6 shows the high-level mapping as part of the data extraction. Table 8 shows how the intervention functions from the previous section (see Table 7) map to the intervention targets.

Table 8 Mapping of intervention functions to intervention targets

COM-B category	Factors	Intervention functions	Studies
Automatic motivation	Mood state / emotional disorder	Education* Enablement Training	Mohr <i>et al.</i> , 2000
Reflective motivation	Beliefs about treatment Self-efficacy	Education Enablement* Persuasion Training*	Berger, Liang and Hudmon, 2005; Turner <i>et al.</i> , 2014
Psychological capability	Cognitive functioning	Education Enablement Environmental Restructuring* Persuasion* Training	Berger, Liang and Hudmon, 2005; Turner <i>et al.</i> , 2014; Zettl <i>et al.</i> , 2016
Physical opportunity	Packaging characteristics of medicine	Education* Enablement Persuasion* Training	Berger, Liang and Hudmon, 2005; Turner <i>et al.</i> , 2014; Zettl <i>et al.</i> , 2016

*denotes where the mapping does not align with recommendations from the BCW (Michie, Atkins and West, 2014).

Mapping of intervention functions to intervention targets

There was an almost even split between which functions and intervention targets aligned, as defined in recommendations from Michie and colleagues (2014) and which didn't, as shown Table 8. Education met recommendations where it was aligned with reflective motivation and psychological capability; however, education was also included in interventions targeting automatic motivation and physical opportunity, which do not match the guidance.

Enablement was congruent with recommendations as it aligned with automatic motivation, psychological capability and physical opportunity, however, its mapping to reflective motivation was not. Training was aligned to all four categories, with only its alignment to reflective motivation being incongruent

with the recommendations. Persuasion was mapped to three categories, one matched recommendations (reflective motivation) but two did not (psychological capability, physical opportunity). The remaining intervention function, environmental restructuring was only mapped to one COM-B category, psychological capability, but this does not align with recommendations from the BCW.

Mapping of BCTs to intervention functions

Whilst there was some discrepancy between the intervention functions and their category targets compared to recommendations from the BCW, specific BCTs were all congruent with the guidance with relation to the relevant intervention functions they align with (see Table 7). Though it is worth noting that whilst there is guidance, the range of BCTs aligned to each function within this guidance is very broad (Michie, Atkins and West, 2014).

Mapping of BCTs to factors

BCW guidance does not, at this time, directly align to BCTs to specific target factors, only to the intervention function level (above) which in turn can then be mapped to COM-B categories. To this end, the mappings described in this section cannot not be reviewed against recommendations in any greater detail than has already been described above,

Mood state / emotional disorder

As described above, the intervention from Mohr and colleagues (2000), whilst it measured adherence as an outcome, was primarily targeting mood state / emotional disorder in MS. A CBT approach was taken, adapted to address some specific factors associated with MS and / or living with a chronic condition that can impact mood. The specific BCTs it was possible to

determine from the intervention description were: Goal setting (behaviour and outcome), discrepancy between current behaviour and goal, action planning, review behavioural goals, framing / reframing, self-monitoring of behaviour, prompts / cues, social support (unspecified).

Beliefs about treatment and self-efficacy

Motivational interviewing techniques were used in both the interventions that sought to address beliefs about treatment and self-efficacy, both of which sit within the COM-B category of Motivation - reflective (Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005). BCTs that were used in both interventions were: instruction on how to perform the behaviour, information about health consequences, pros and cons and social support (unspecified). Berger and colleagues (2005) also included framing / reframing. Turner *et al.* (2004) included an additional nine BCTs: prompts / cues, self-monitoring of behaviour, action planning, problem solving, feedback on behaviour, salience of consequences, commitment and goal setting (behaviour and outcome).

Cognitive functioning (forgetting)

Two interventions sought to address forgetting through the use of prompts/cues, namely reminders delivered electronically (Zetl *et al.*, 2016) or follow-up calls when potential non-adherence was evident (Turner *et al.*, 2004). Both interventions also included self-monitoring of behaviour and instruction on how to perform the behaviour. In addition, action planning, problem solving feedback on behaviour, information about health consequences, salience of consequences, commitment, goal setting (behaviour and outcome), discrepancy between current behaviour and goals, pros and cons and social support (unspecified) featured in the Turner *et al.* (2004) intervention.

Three of the interventions offered support to reduce / manage injection site pain (Zetl *et al.*, 2016; Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005). There was only one consistent BCT that featured in all of them which was instruction on how to perform the behaviour. Information about health consequences, social support (unspecified) and pros and cons featured in both the MI based interventions (Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005). As described above, prompts and cues and self-monitoring of behaviour were also features of the PDA intervention (Zetl *et al.*, 2016) as well as Turner and colleagues (2014) MI based support. Action planning, problem solving, feedback on behaviour, salience of consequences, commitment, goal setting (behaviour and outcome) and discrepancy between current behaviour and goal were also included in the Turner and colleagues (2014) intervention. Framing / reframing was featured in one intervention targeting injection site pain (Berger, Liang and Hudmon, 2005).

Mechanisms of action - link between positive impact on addressed factors and adherence outcomes

As outlined in the BCW, successful behaviour change is more likely to occur when interventions are designed specifically to address identified facilitators or barriers to the desired behaviour (Michie, Atkins and West, 2014). With reference to factors appearing in the COM-B for adherence to DMTs in people with MS, only mood state / emotional disorder and self-efficacy were explicitly measured (Turner *et al.*, 2014; Mohr *et al.*, 2000), with a positive change only evident in mood state / emotional disorder. Mohr and colleagues did not explore whether there was a statistically measurable moderation or mediation effect of the factor on intervention outcomes.

Discussion

The overarching aim of this two-part scoping review was to understand the level of congruence between research exploring factors related to adherence to DMTs in people with MS and behaviour change intervention research to address these factors. As it is widely acknowledged that adherence research methods, terminology and intervention design / implementation can be fairly heterogeneous (Michie, Atkins and West, 2014; Pound *et al.*, 2005; Vermeire *et al.*, 2001) the findings were operationalised using the BCW to aid comparison across studies and to help explore the applicability of current models of health behaviours and adherence (i.e. SRM, COM-B for adherence) for people with MS.

This discussion comprises the following sections: discussion of findings aligned to the research questions; reliability, rigour and trustworthiness of the data, review of methods and models applied; summary and implications for future research.

Discussion of findings

Factors influencing adherence to prescribed DMTs in people with MS

During data extraction from the studies looking at reasons for non-adherence, sixty-nine discrete factors were identified across thirty-three studies. Twenty-nine of these were reported more than once and could be grouped into five descriptive categories: clinical; demographic; opportunity; treatment; and psychosocial. This high number of discrete factors found across the studies supports the position of Vermeire and colleagues (2001) that much of the research into drivers of adherence is doing little to advance our knowledge,

despite the relatively high number of studies. They describe how over 200 different factors have been studied, yet there is a definite lack of consistency in terms of predicting outcomes, partly due to reductive and inconsistent methodologies, but also, it is proposed, due to the ideology that frames adherence research in general (Vermeire *et al.*, 2001). As described earlier, whilst efforts have been made to change the terminology relating to adherence research (from notions of passive compliance to healthcare professionals and systems, to language that is more conducive to shared decision making and the active role of the patient in their not only their healthcare behaviours but also what constitutes desirable, meaningful outcomes for them) it is proposed that research into adherence does not appear to have adapted to this change (i.e. shifted its ideology) (Pound *et al.*, 2005; Vermierre *et al.*, 2001) other than to edit the terminology used. Findings from this review support this position as, whilst many researchers described their studies as exploring adherence (a term used to imply that a level of prior agreement has been reached between a patient and their healthcare provider), the majority of methodologies used fundamentally failed to seek to understand how involved the patient had been in treatment decision making processes. Furthermore, out of the thirty-three publications that were reviewed, only a small minority ($n = 2$) provided any opportunity for people with MS to provide their own reasons for not wishing to take treatment, and even these opportunities were limited to one or two open field responses within survey questionnaires. The rest of the factors were pre-determined, either through data that was available in clinical notes / databases or by the use of closed surveys and structured interviews. The relatively high number of factors that encompassed 'unmodifiable' clinical or demographic variables,

also suggests a lack of consideration of the lived experience of MS and the complex nature of self-regulation of health (Leventhal *et al.*, 2016). Research such as this can be considered useful for highlighting people more 'at risk' of nonadherence but does little to help grow our understanding of cognitive and perceptual processes or any practical barriers that may be mediating these outcomes (Allemann *et al.*, 2016). As these are the components which are potentially modifiable through appropriate intervention and support, it is possible to see how many of the current approaches to understanding non-adherence in people with MS may not be cognizant with research that seeks to modify behavioural outcomes.

The large number of study variables also suggest that much adherence research in MS has not been built on prior findings (as it would be hypothesised that this would reduce the number of variables over time) and therefore there has been apparently little advancement in understanding since the launch of DMTs in 1993.

Operationalisation of MS adherence research factors to COM-B

To aid comparison across studies, synthesis of results, and potential for future replication of findings, prevalent (appearing more than once) adherence factors were operationalised using the COM-B for adherence (Jackson *et al.*, 2014) as a reference point. When operationalised to the COM-B model of adherence, less than 50% of variables could be mapped. Those that couldn't be mapped directly were primarily demographic and clinical factors (referencing the original data extraction categories), such as relapse features, level of disability, age and gender. This also meant that there were ten factors from the COM-B model for adherence (Jackson, *et al.*, 2014) that did not

appear in this research, across all category domains. These findings are discussed in line with COM-B categories below.

Capability (psychological)

One factor from the review mapped to psychological capability, forgetting, aligned with cognitive functioning. In their model, Jackson and colleagues (2014) actually exclude forgetting as a variant of cognitive functioning as they posit that there is more of an interplay between perceptions of treatment necessity (where not enough importance is placed on 'remembering') and forgetting than the category suggests. This is further supported by literature examining the interplay between intentional and unintentional adherence, which proposes that they are not two distinct domains but are often related to each other. In particular demonstrating a positive relationship between motivation to adhere and remembering to do so (Gadkari and McHorney, 2012). An element of social desirability, whereby it can be perceived as more acceptable to say you have forgotten rather than admit to 'not wanting to' is also believed to undermine the validity of this factor (DiMatteo and DiNicola, 1982). However due to the cognitive limitations that are often experienced as a direct result of MS I felt it was not only feasible but also important to include this as an explicit factor within Capability. In addition, the structure of COM-B acknowledges the interplay between categories, so this element is not lost from its inclusion as an explicit factor within cognitive functioning.

Interestingly, considering the often significant impact on cognition and executive functioning of MS, there was not significant evidence from these studies of the role of diminished cognitive functioning on adherence.

Increased disability did feature, but this appeared to be primarily related to physical decline rather than mental. As described earlier, reduced capacity

can not only increase chances of forgetting but can also impair ability to put plans in place to mitigate it. Furthermore, if we look at the proposed tenets of the process of self-regulation, whereby coping procedures are driven by cognitive process, such as memories, coherence and forming mental representation, then reduced cognitive capacity may not only be impacting adherence 'directly' but also through impeding the general processes of self-regulation as well.

Comprehension of disease and treatment, a factor included in the Jackson and colleagues (2014) model was not evident from this research, though it should be noted that this was rarely explicitly explored rather than being a 'negative' finding. Whilst it is widely acknowledged that education alone is not enough to change behaviour (Haynes, 1996) it is recognised that having a core understanding of your illness and treatment is a fundamental underpinning to self-management (Moss-Morris et al., 2002), so as mentioned above, it's omission is likely to be related to it not being examined, as opposed to it not being applicable to people with MS.

Capability (physical)

Through the direct mapping process, no factors appeared in this category as explicitly reported in the review studies. Due to the potentially comprehensive nature of physical limitations in MS, as with cognitive limitations, this was a surprising finding. The extent of findings relating to physical characteristics of medicine, such as oral preference and injection site pain mean that dexterity, as featured in the original COM-B for adherence is 'likely' to be factor influencing this, but the evidence does not explicitly support this. Increased level of disability did feature in the review findings and was therefore mapped to this category in the MS specific COM-B. Whilst this would certainly

encompass 'physical capability to adapt to lifestyle change' from the original model, the measures used in the studies were not explicit enough to bring this across. Instead, due to the variability of the measures used it features at a more holistic level, acknowledging the role of disease progression on general ability to self-manage.

Motivation (reflective)

Considering the wealth of research demonstrating not only the relevance of illness perceptions on adherence behaviours (Kucukarslan, 2012), but also their potential for modification to influence adherence outcomes (Broadbent *et al.*, 2009; Petrie *et al.*, 2002), it was surprising to see that illness perceptions did not feature. However, as with comprehension, they were not really explored in the research, despite being operationalised for quantitative research through measures such as the illness perception questionnaire (IPQ, Moss-Morris *et al.*, 2002).

Treatment perceptions, however, were evident from the review and treatment variables in general were extensively explored. Concerns (including side-effects) and perceptions of efficacy were the two factors from the original model that could be mapped directly. Due to the quantitative nature of the research it is difficult to determine the extent to which the findings that mapped to concerns were experienced (e.g. adverse events) versus perceptual (e.g. long-term impact on body). However, evidence relating to the utility of the 'Necessity-Concerns framework' (Horne *et al.*, 2013; Horne, Weinman and Hankins, 1999) in predicting adherence and the 'logic' of coming off treatment when experiencing adverse reactions suggest that it is likely a combination of both. Conversely, the other 'side' of the framework, necessity, did not explicitly feature in this research as a driver of adherence.

Berger and colleagues (2004) did explore 'pros and cons' of treatment, but conceptually it is difficult to confidently map this to necessity, as needing a treatment may not be perceived as a positive thing. Pros of treatment is more likely to incorporate perceptions of efficacy, which did feature as an explicit factor. Interestingly, whilst perceptions of efficacy were an apparent driver in this research, a closely related factor, outcome expectancies, was not. These are important to consider together as perception of efficacy is contingent on having appropriate expectations about what the treatment can do (Mohr *et al.*, 1996). This also relates to the comprehension of treatment from the capability category.

Self-efficacy was another factor from the original model that was cognizant with findings from this review. Self-efficacy is a key tenet of chronic disease self-management research and support, built on a strong foundation of behavioural research into the role of confidence and the execution of health behaviours (Lorig *et al.*, 1999; Bandura, 1982). Whilst self-efficacy is a discreet concept, it is seen as one of the underpinning 'dynamic' mechanisms within the SRM. So, as well as low self-efficacy being a 'flag' for potential risk of non-adherence, trying to understand in what way it influences behaviour (e.g. what skills do highly self-efficacious people employ? What prevents people from feeling confident to execute behaviours?) can also help to understand how best to address it (Leventhal, Phillips and Burns, 2016).

Hope was an additional factor that mapped to this category, whereby a greater sense of hope for the future with MS resulted in better adherence outcomes. Hope is not a specific illness perception with the SRM but may tie into beliefs about future consequences and sense of personal control over the illness and has been shown to have a close association with both motivation and positive

coping, underpinned by mental representations of health (Lloyd *et al.*, 2009; Maikranz *et al.*, 2007).

Finally, quality of life (QoL) was another factor that was added to reflective motivation based on the findings of the review. Frequently, quality of life is used as an outcome measure to determine illness impact as opposed to a driver of illness related behaviours (Rabin and de Charro, 2001). However, common QoL domains include physical functioning, social functioning and mood, so it is possible to see how this is potentially aligning with other variables within the COM-B model.

Motivation (automatic)

This review did demonstrate the role of mood state / emotional disorder on adherence. This is in line with research which has demonstrated that depression and low mood are consistent drivers of non-adherence (DiMatteo, Lepper and Croghan, 2000). Additionally, further research has shown that reducing emotional affect often translates into better self-management outcomes, including adherence (Lorig *et al.*, 1999). With relation to self-regulation, it is recognised that the emotional response to an illness threat will also influence coping procedures as well as cognitions (Moss-Morris *et al.*, 2002). Stimuli / cues for action did not feature as an explicit factor.

Opportunity (physical)

This was the most prevalent category in terms of number of individual factors and is likely related to the high number of studies that explored treatment variables. In particular studies sought to explore oral versus injection administration as a driver of adherence and this is evident from the number of factors sitting within the sub-category of 'packaging characteristics of

medicine'. Injection-based treatments do have considerations that are not applicable in oral treatments, such as injection pain, injection site reactions, and greater inconvenience. As described earlier, in MS, some of these features are likely compounded by motor-function difficulties (Jopson and Moss-Morris, 2003) making self-injection more burdensome through dexterity issues, enhancing the likelihood of factors such as injection fatigue, anxiety and pain (from incorrect use). Whilst the majority of factors that were categorised in this review as treatment related could be mapped to the COM-B model for adherence, the broad range of potential variables and as proposed by the general tenets of the COM-B model (Michie, Atkins and West, 2014) changing the treatment administration method may have an impact for some people but will not address other potential issues, in particular motivational factors that are not related to the treatment type. Interestingly, one study did demonstrate that it is possible to increase perceptions about the pros of treatment, leading to better adherence, without necessarily reducing perceptions about the cons (Berger, Liang and Hudmon, 2004). Therefore, removing potential barriers (such as method of administration) may only be effective if the perceived benefits are strong enough to motivate treatment use in the first place. Dosing was another treatment factor that appeared across a number of studies, with overwhelmingly greater frequency of dosing leading to greater likelihood on non-adherence, though some studies simply referred to 'inconvenient dosing' rather than relative frequency. In general, the literature on impact of dosing is cognizant with this finding (e.g. Weeda *et al.*, 2016) but as with administration features, reduction in dosing alone may not be enough to drive adherence for all people if other factors, such as perceived benefit, are not in place.

Other physical opportunity factors were, cost of treatment, physician support of treatment choice and caregiver support and congruence with choice. Considering the comparatively consistent evidence of the impact of the therapeutic relationship on acceptance of and adherence to treatment (Fuertes *et al.*, 2015), this relationship was infrequently explored in the studies identified and the questionnaires focussed on physician support of the treatment as opposed to congruence between patient and doctor, communication or satisfaction with relationship. In terms of social support, practical elements, in particular administration of injections from 'caregivers' were prevalent, reinforcing the idea that increasing physical disability may impact adherence through dexterity issues. In addition, general caregiver support, in terms of agreement with treatment and the provision of general support was also evident, in line with other research in MS (Siegel, Turner and Haselkorn, 2008).

Cost was also a factor from the original COM-B that featured in these studies. Cost, from a patient choice perspective, is market specific. It has been shown to be an important consideration both from a practical perspective in terms of real affordability and from a perceptual perspective in terms of relative value placed on medicines over and above other expenditure (Eaddy *et al.*, 2012).

Travelling was a factor that some patients referenced as a barrier to adherence but does not feature in the general adherence COM-B. As mentioned earlier, cognition problems may make putting alternative plans in place to mitigate risk factors or travelling (such as being away from their standard environment reducing cues for action) as well as the loss of stimuli directly increasing likelihood of non-adherence. Access (availability of medicine) did not feature as a discreet factor in this research.

Opportunity (social)

There were no factors from this review that could be mapped to the category of social opportunity. Whilst social elements appeared in the form of the caregiver and HCP variables featured in physical opportunity, this category refers to the broader social 'landscape' that may influence behaviours or motivation. Specifically, within the COM-B model for adherence this includes 'stigma of disease, fear of disclosure' and 'religious / cultural beliefs'. As with many of these factors, it may be more related to the lack of exploration of these factors than it not being relevant to this population. The role of stigma to negatively influence adherence has been investigated and demonstrated across chronic conditions, in particular areas such as HIV (Katz *et al.*, 2013) and mental illness (Corrigan, 2004) where the social stigma is seen as relatively pervasive in society. With relation to MS, stigma has been shown to negatively influence adjustment and acceptance (Dennison *et al.*, 2010) and the use of injection-based treatments, particularly for adolescents has been shown to be perceived as stigmatising (Thannhauser, Mah and Metz, 2009). Similarly, there is a body of evidence relating to the impact of cultural and / or religious beliefs to self-management and adherence. This can be through its direct influence on perceptions of illness (Borras *et al.*, 2007) or the impact that cultural structures have on availability of social support (Hatah *et al.*, 2015). Leventhal and colleagues state in their relatively recent paper that, *"The relationship of social factors to the formation of prototypes of diseases and specific treatment procedures is an open area for study"* (Leventhal, Phillips and Burns, 2016, pp. 941), supporting the assertion that this may be a relatively un-explored area in specific relation to impact on illness and treatment representations and self-management behaviours.

Factors from the review that could not be mapped to COM-B categories

From the original data extraction, a range of factors could not be mapped, these were from the clinical and demographic categories. With regards to clinical features, such as number of relapses, it could be argued however that these will be part of the mechanism of action of the SRM as these are features of the threat itself. Symptom profile (including no. of relapses) is linked to illness identity beliefs (Moss-Morris *et al.*, 2002) and may also reflect actual or perceived treatment efficacy (Horne and Weinman, 1999). An individual may perceive fewer relapses as evidence of treatment working and decide to continue taking it (Jopson and Moss-Morris, 2003). Conversely, they may perceive fewer relapses as evidence of an improvement in disease and decide that treatment is no longer required or choose to 'experiment' with dosage to see if it is still needed (Pound *et al.*, 2005; Jopson and Moss-Morris, 2003). When explored at this level, it is also possible to see why number of relapses garnered different results in different studies, in terms of direction of effect. As can be seen with just this example, there can be a range of individual, patient driven factors that change the 'outcome' behaviour following the same pre-cursor clinical factor and it is the understanding of these that may be more conducive to focussing behaviour change interventions.

The same 'logic' can be applied to demographic factors, such as gender and education level, which both showed mixed results. Being of 'older' age was a consistent finding across the studies. With a progressive condition such as MS, older age and a longer time since diagnosis will often be accompanied by a worsening of the condition (more relapses, greater disability), and as

described above, it can be posited that it is how the individual represents these changes cognitively that drives health related behaviours, including adherence to treatment. Of note is that there was no common definition of what age constituted 'older' – it was often reported as the direction of the range of age on a continuum. Where age categories were used, these varied across studies, restricting alignment. Therefore, the data in terms of who is at greater risk of non-adherence based on age is also not clear and it can be proposed, that it is also certain factors associated with older age, rather than age per se which is causing the 'relationship' to be found. An example is the risk of unintentional non-adherence through forgetting may become a greater risk when there is more disease progression, related to time with disease, having a negative impact on cognitive function.

[Relationships between factors](#)

As described above, in the context of adherence, COM-B is proposed to be a useful behavioural framework as it allows for consideration of both intentional drivers of non-adherence (e.g. illness and treatment perceptions as outlined in the SRM) and unintentional barriers, such as cognitive limitations or physical access to treatment. As well as allowing for both 'types' of behavioural facilitators / barriers to be considered, it also hypothesises the potential relationships between categories (Capability, Motivation, Opportunity), thereby recognising the dynamic nature of adherence behaviours, not only between individuals, but 'within' individuals as their experiences change over time. Whilst COM-B is designed to be theory agnostic (Michie, Atkins and West, 2014), in relation to adherence, it is possible to see how the framework supports the 'extrapolation' of the different levels of perceptual, cognitive and behavioural processes proposed to be influencing health self-regulation as

described by Leventhal and colleagues (2016) and, crucially, further aid our understanding of the 'why' of non-adherence . For example, perceptions of treatment efficacy may directly influence motivation to adhere, but for one individual they may be best addressed through increasing psychological capability (i.e. knowledge and understanding) rather than directly trying to influence motivation by encouraging objective monitoring of treatment outcomes.

Factors modified through intervention

As described above, there were significantly fewer studies identified which focussed on adherence interventions, and even less that demonstrated a positive impact through the targeting of factors, identified in the first part of the review.

Three of the interventions proposed to target psychosocial as well as treatment variables (Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005; Mohr *et al.*, 2000) and all of the interventions examined at least one psychosocial outcome alongside adherence. All of those that stated an explicit focus on psychosocial variables used 'therapy' style interventions, drawing on either CBT or MI principles. The interesting thing to note about this style of intervention is that it is very individualised. Whilst they work within a framework, they can be flexible to the situation and reactions of the person receiving the intervention (Miller and Rose, 2009; White, 2001). Therefore, they are likely to be able to explore the incidental and mediating considerations to identify the *why* behind certain behaviours (Rothman, 2004) as well as eliciting personal values and offering practical support to boost motivation, confidence and ability, leading to the successful outcomes

demonstrated. These interventions also seek to promote the learning of a set of skills, which will support not only adherence behaviours but other self-management requirements too.

Whilst building on the same framework, the two MI based interventions were very different and it could be argued that the intervention by Turner and colleagues (2014) demonstrated the positive impact of reminders and follow-up, rather than MI due to its design. In addition to initial MI sessions, participants were provided with a home monitoring device to record their adherence with. Whilst the reminder function was optional, if notification of treatment compliance was not received, participants received a follow-up call. It could be argued that this is still working as a reminder, simply after the fact. The follow-up calls were delivered by a study therapist trained in MI, however, there was no significant impact on the psychosocial factors posited to be influencing adherence, in particular self-efficacy, which is a key tenet of MI. In addition, there was no follow-up to explore the maintenance of adherence behaviour once the intervention was complete. This is in comparison to a study conducted looking at the impact of illness representations on adherence in asthma. They were able to demonstrate a positive impact on both beliefs and adherence through a tailored intervention targeting illness representations (Petrie *et al.*, 2012). Both outcomes were maintained once the explicit intervention had stopped, suggesting that the targeting of underlying belief drivers can promote better self-management. This is in comparison to 'reminder' style interventions that may help reduce forgetting whilst in place but fail to account for the interplay between forgetting and motivation (Gadkari and McHorney, 2012) and therefore demonstrate limited success in maintaining positive behaviours.

In comparison, Berger and colleagues (2005) describe a more 'traditional' MI intervention that did not include reminders or monitoring and were able to demonstrate a positive impact on stage of readiness to stop treatment, treatment importance (necessity) and self-efficacy², as well as the primary outcome of persistence. However, they did not examine persistence rates beyond the timeframe of the intervention either, so it is not possible to determine if these changes would persist post-intervention. An interesting finding from this study was that through a focus on individual pros and cons of treatment, they were able to demonstrate a significant increase in pros, but this was not matched by a significant decrease in cons. As stated earlier, this is an important observation because often the cons of treatment cannot be removed (e.g. injection site pain, side effects) or changing treatment is seen as a 'quick fix' but does not address alternative, 'underlying' issues.

The CBT based intervention was the only one that measured, and therefore demonstrated, impact post-intervention (Mohr *et al.*, 2000). It primarily sought to improve levels of depression, for which there is strong evidence for the use of CBT (Butler *et al.*, 2006) and had demonstrated this at the end of the eight weeks of support. At four months, they were also able to demonstrate greater levels of persistence in the intervention group, compared to the wait control group. Whilst the relationship between the two outcomes was not explored statistically, the apparent impact on treatment behaviours from the reduction of emotional negative affect supports the findings not only of this review but

² The self-efficacy scores were not available in the publication, though the discussion states a positive impact on this factor.

also of previous research in this area (DiMatteo *et al.* 2000). However, as proposed above, it could also represent the benefit of providing individuals with the appropriate skills to manage the multiple demands of living with a chronic condition, allowing for positive outcomes in relation to a number of behaviours and outcomes.

The single intervention that did not use a therapy style intervention demonstrated a moderate impact on dosing adherence with the use of a PDA plus reminder, compared to PDA without reminders. However, these numbers were within the range of 'comparable' adherence data for people with MS, rather than demonstrating exceptional results (Zettl, et al., 2016). This intervention aimed to target treatment variables, such as injection site rotation, signposting to information on side effects, as well as providing reminders to one intervention group. There was no focus on psychosocial factors, and it demonstrated no impact on psychosocial outcomes, such as depression and quality of life. Neither did improved adherence translate into a reduced number of relapses.

BCW and theoretical underpinning

Behaviour change theories and models

In line with recommendations regarding the development of complex interventions (Craig *et al.*, 2008), three of these interventions referenced a behavioural model or theory. It is proposed that this is important to aid intervention design as it allows for the iterative development of them from prior theory and evidence synthesis, thus building on knowledge as opposed to simply doing what 'seemed like a good idea at the time. Additionally, it starts

to take us towards an understanding of what the mechanisms of action may be within these theories and models that influence behaviour, as well being a way to empirically 'test' these theories (Michie, Atkins and West, 2014). In this review, only one study cited building on a previous 'exploration' of the model specifically for their population and behaviour (Berger, Liang and Hardmon, 2005), whilst the other two relied on the weight of evidence relating to the intervention techniques themselves (CBT and MI), (Turner *et al.*, 2014; Mohr *et al.*, 2000). Whilst some of the studies from the first review utilised a theory base for their exploration of drivers of adherence (e.g. Fraser, Hadjimichael and Vollmer, 2003) many did not, and this may go some way to explain the wide range of factors found across the studies and the relative incongruence between the two parts of this review.

Policy categories

As these interventions were developed in the context of research, as opposed to broad intervention implementation (e.g. developing standards of care within an NHS setting), the policy mapping exercise had to be fairly broad and high level as, whilst studies referred to the potential applications of their findings, none went specifically into details of what would be needed to implement them further.

Behaviour change techniques

Across the four interventions, there were sixteen BCTs identified, though none of the studies explicitly referenced the taxonomy (however, due to publication dates, only Zetl *et al.* (2016) could have reasonably done so). Many of the BCTs were repeated across the studies and overwhelmingly the intervention descriptions were clear and detailed enough to be able to determine which BCTs were being applied. This was further enhanced by the fact that three of

the studies used a recognised intervention framework and theoretical basis from which standard techniques could be elicited, as discussed above. The prevalent BCT categories for the therapeutic interventions were: goals and planning, feedback and monitoring, natural consequences, comparison of outcomes and identity (Abraham and Michie, 2008). As described above, Zettl and colleagues (2016) did not attempt to address psychosocial factors, other than forgetting, and therefore the BCTs used were limited to feedback and monitoring and associations. All interventions included 'additional' features which intended to shape knowledge and, whilst increasing social support was only an explicit aim in one of the interventions (Mohr *et al.*, 2000) by their nature all three of the therapeutic based ones may have had a positive impact on support perceptions through the use of call centre staff / therapists who regularly interacted with participants.

Reliability, rigour and trustworthiness of the data

Review 1 – Factors impacting adherence in people with MS

Overwhelmingly, data was collected using structured surveys or via clinical / treatment databases. This meant that the majority of data collected was restricted to clinical, demographic and treatment factors that are available through such databases or that survey responses were limited to components determined by the a-priori aims and assumptions of the research, again often treatment or clinical in nature. As described above, these studies can be useful in determining certain 'risk factors' for non-adherence but are often restricted in the number of modifiable factors they produce (Allemann *et al.*, 2016) due to their restrictive nature in terms of what is available. These methods also restrict the likelihood of generating novel findings as, to some

degree, it is data of convenience in terms of being relatively easy to access and analyse, compared to trying to collect data on a broader, perhaps more complex, range of factors.

In addition, whilst clinical and prescription databases can be considered fairly robust sources of data, the use of secondary sources of data, as opposed to the collection of primary data specific to the study aims will generally carry more risk of non-reliability.

The time span of the search meant that there were a number of studies that looked specifically at the impact, or potential impact, of the development of new oral therapies in a market that was previously restricted to injection and infusion delivery methods. Therefore, there is potentially a bias in the results towards treatment related factors, which were the most prolific category in the initial data extraction. Whilst undoubtedly a salient consideration in relation to adherence, the prevalence of a wider range of factors that appeared in studies that had 'broader' investigations demonstrates the risk of missing other considerations with such a narrow research focus. For example, Hupperts and colleagues (2014) demonstrated that even with a fairly limited number of survey response options about treatment, there were 5 variants that came out as important (injection anxiety, pain, side effects, fatigue, efficacy). This not only speaks to a level of complexity beyond the dichotomous proposition of 'oral versus injection' but also shows the potential for variance between patients, based on their own experiences and treatment trajectories.

The variations across the studies in terms of methodologies and what constitutes appropriate adherence, suggest that there is an opportunity to conduct a full systematic review and, if possible, a meta-analysis to help determine the relative 'weight' of the varied findings. This may help to narrow

down the findings, which as discussed above, are currently disparate and adding little value in terms of the focus for adherence-based interventions. Furthermore, as a number of the findings were inconsistent, it would be useful to follow the methods of similar review (Johnston *et al.*, 2016) which explored the number of times factors had been studied and how often it showed both a positive and a negative correlation (e.g. non-findings) as this may help to mitigate the bias towards factors that appear more frequently due being measured more frequently.

A lack of consistent terminology was evident across the studies, as was a lack of consistent definitions (e.g. what constitutes 'older' age) and there was hardly any evidence of the use of categories to help group different factors, beyond clinical and demographic. The implication of this finding is that current research into adherence in MS is not helping us to narrow down the potential factors for consideration because it is very difficult to draw confident comparisons across studies. This also supports the 'aspirations' of initiatives such as the BCW to provide a common language that can be applied to behavioural research so that findings can be compared and built upon (Michie, Atkins and West, 2014).

Review 2 – MS adherence factors successfully targeted though intervention

With exception of Zettl (2016) the interventions were tested against standard care, so this makes it difficult to narrow down which of the intervention elements were having an impact. This is particularly relevant for Turner and colleagues (2014) as whilst it used an MI methodology, as described above, this was supplemented by an intensive reminder intervention; following up each time adherence was not recorded. This design, plus the lack of impact on psychosocial outcomes, makes it unclear as to whether it was MI per se

that was having an impact, or the reminding, follow-up and general social support. As noted by the authors themselves, research that looks at the role of MI with and without home monitoring could help us to understand the 'why' of the successful intervention. Additionally, whilst it was possible to map the BCTs that featured in an intervention 'as a whole' there was no mapping process within the descriptions to state what different parts of an intervention were targeting in particular.

As with the first part of the review, despite the relative small number of successful intervention studies identified, there was still a lack of consistency between them. Timeframes were different, making it difficult to understand temporal implications and only one study sought to understand the impact of the intervention post completion. As seen in the first part of the review, definitions of adherence varied between studies and were measured differently.

Only one study described their adherence findings in the context of population level data. So, it was possible to determine the effect between their sample groups but not if these findings were comparable or 'better' than adherence rates in the general MS population. The one study that did do this, found their data to be comparable to population adherence, as opposed to better than.

The use of a theoretical and intervention framework base was evident in the majority of the studies, making categorising the interventions with the BCT taxonomy possible. However, only one study attempted to explicitly describe how their intervention mapped to the theoretical approach. As a proposed

advantage of using a theoretical framework within an intervention is to 'test' the hypotheses of the framework, providing a more detailed link between the two components and presenting results in the context of what it means in terms of its theoretical basis could help to increase our understanding of the applicability of these theories and refine them in light of 'real world' experiences.

It was not within the scope of this review to interrogate the rigour or validity of the research designs and / or fidelity of intervention delivery. To this end, caution must be applied in terms of the overall validity of these findings, particularly if considering the two parts of the review independently of each other (e.g. this thesis is not intended to provide a definitive answer on what drives adherence in MS, or how adherence in MS should be addressed, it is intended to understand the level of congruence between the two areas of research and what is already known about this phenomenon). To this end, as described above, there is definitely scope to conduct a systematic review and / or meta-analysis to try to reach a more concrete understanding of adherence drivers in MS.

Review of methods and models applied

Scoping review

The purpose of a scoping review, as described earlier, is to allow for the rapid mapping of key concepts from a particular research area of interest. It can be useful as a starting point to understand gaps in knowledge that may then warrant more robust investigation, as opposed to a systematic interrogation of an issue, even though the methods themselves are still systematic in nature

(Arksey and O'Malley, 2005). To this end, the review methodology applied would still seem to be valid in the context of this research question and has helped to demonstrate the relative incongruence between the two areas studied. However, the amount of data from the first review was unexpected and with more data, comes a greater risk of error and misinterpretation, particularly as this review was conducted independently. As described above, this area in particular (drivers of non-adherence in people with MS) would benefit from a more rigorous examination of the data, in particular applying more restrictions to the type of studies included and the application of quality criteria to the studies. This would not only increase the trustworthiness of the findings of the first review in relation to its specific question but may also reduce the number of variables that are found.

With regards to the second part of the review, factors modified through behavioural intervention, similar limitations apply, though the significantly reduced amount of data, not just in terms of number of studies but also in terms of what was reported, reduces the likelihood of data errors in terms of reported results.

Additionally, non-impactful interventions were excluded due to the specific objectives of this review, but the size of the final sample of included interventions suggests that it would advance our understanding to know what is being targeted, how it is being targeted and what is NOT working, as these insights may also help inform design considerations for adherence interventions.

This review did not explore the different settings of the interventions or consider the practical application in usual care. This is important, as ideally,

potential interventions should be able to be implemented alongside standard care to help ensure uptake and dissemination as widely as possible.

Use of the BCW to synthesise findings

The broad range of factors found in the first part of the review necessitated the grouping of these factors to aid description, even before they were operationalised through the COM-B model for adherence. Overall, I felt that utilising the COM-B categories made it possible to gain even further clarity on the findings, though this may have been helped by my familiarity with the model and the fact that I use it regularly to synthesise adherence research and guide behavioural intervention design. Therefore, whether the process would have been as 'clarifying' for someone not as familiar with the model, I cannot say.

As I worked on this review independently, there was only a single analysis and labelling of the factors and intervention components which, whilst the descriptions were, overall, clear and reasonably detailed, this still required an element of interpretation to determine the exact BCTs employed, (e.g. which aspects of goal setting, which aspects of 'mindfulness') and to try to align factors from the review to categories and features already within the adherence COM-B. I have been trained to undertake intervention coding with the BCT taxonomy, but the lack of interrater reliability and the fact that the studies themselves did not use this terminology means that the mapping may not be wholly accurate – though I am confident that the methods employed were rigorous enough to be able to stand behind the overall 'story' of this review. In addition, the 'pre-defined' nature of the COM-B for adherence may have meant that associations were made due to an element of priming, that

may not have occurred if labelling was done independently from the model (e.g. only using category descriptions).

The discrepancy between the factors found in this review and those proposed in the 'original' COM-B for adherence suggest that trying to define specific models for specific behaviours may be a challenge, particularly in areas subject to as many heterogenous population types as adherence. However, the categories within the COM-B do appear to have served their purpose in allowing for the consolidation and consideration of the different 'types' of factors to consider. For example, through the process of creating a COM-B specifically for adherence in MS, it was evident that all three areas (capability, motivation and opportunity) were having an influence and it also allowed for hypotheses to be drawn on the potential relationships between factors. Furthermore, it helped to define where the findings supported the use of the extended SRM as a model for understanding adherence behaviour and where they did not.

As stated earlier, COM-B is designed to be theory agnostic, and even though the adherence version from Jackson and colleagues (2014) incorporated illness and treatment representations, by using it as a way to categorise and explore congruence, findings were able to be described 'beyond the models' but still in a meaningful way. For example, I feel that aligning novel factors such as hope and travelling to their relevant categories means that this research is building on previous insights – these factors don't just become another thing on a 'list', they are contributing to the development of an MS specific version of a model that has been built on decades of behavioural research.

The inability to map 'non-modifiable' determinants of adherence, such as demographic factors, does potentially reduce its utilisation as a method of distilling a body of adherence research as a whole. Whilst it could be argued that if something cannot be changed it does not need to feature in a behavioural model, the fact remains, as evidenced by this review, that a lot of adherence research currently explores these categories of non-adherence. Furthermore, whilst we may not be able to modify them, they are still 'telling us' something about the population we are trying to understand and potentially support. As described by Allemann and colleagues (2016), at a time where healthcare resources are increasingly under pressure and the incidence of chronic conditions continues to rise, being able to determine which population 'types' are more at risk may aid prioritisation of intervention focus and delivery, with behavioural factors then being utilised to understand what needs to be targeted *within* these populations.

In this review, I feel that the policy and intervention function components of the BCW did not contribute in terms of helping to understand or categorise the interventions or assessing their potential effectiveness. In relation to policies, it seems that these elements are more for consideration for deployment of interventions, as opposed to being a way to categorise them, particularly when looking at interventions that have been delivered as 'research' rather than at the system level. With regards to intervention functions, it was not clear to me what insight these added over and above the BCTs themselves, particularly as some of the mappings proposed in the guidance did not make 'common sense' to me. For example, providing a reminder service as per the PDA intervention (Zetl *et al.*, 2016) constitutes 'environmental restructure' (changing the physical context) and yet it is not aligned in the

guidance to psychological capability, whereby prompts such as these may help to mitigate cognitive challenges. The BCW does not claim to be a fixed blueprint, so to this end, it may be reasonable to expect differences to be found, but as with trying to determine a specific COM-B for adherence 'overall' perhaps it is enough to have the common names and descriptions of intervention functions available to facilitate description, rather than becoming too reductive and trying to pre-determine all the relationships.

However, I did feel that being able to describe the interventions utilising the BCT Taxonomy aided the review, as it facilitated exploration and description of the specific components being used within each one. For example, the intervention that defined their intervention as MI based (Berger, Liang and Hardmon, 2005) but, when looking at the specific pieces of the intervention, it was possible to determine that a large part of the intervention was actually utilising the BCT 'prompts and cues' by calling people when non-adherence was detected. This in no way undermines the intervention, but I feel that this process of trying to define each of the discreet components does help to minimise 'assumptions' being made about what is being delivered. Similarly, being able to group BCTs by categories allowed for distillation of findings into more generalisable hypothesis. Such as the prevalence of 'goals and planning' techniques across studies addressing treatment beliefs or the application of 'shaping knowledge' techniques to support reduction in injection site pain. As described above, being able to map specific BCTs to specific targets 1:1 was not possible due to the way the interventions were reported, they had to be considered as a whole. To this end it is also possible to see the value of utilising the BCT taxonomy to describe interventions, not only to aid transparency and the aggregation of knowledge across research, but also to

prompt more 'thinking' about how the intervention is hypothesised to work at this component level.

Self-regulatory model

The findings from this review went some way to supporting the SRM, though a key component of the model, namely illness representations were not evident from the factors review, in terms of determinants of adherence behaviours. Treatment representations, specifically concerns and efficacy beliefs, were included in the revised COM-B for adherence in MS and therefore support Leventhal and colleagues (2016) proposal that, for adherence behaviours, the model can be extended to include specific representations about treatment. It may also suggest that, for adherence, treatment representations play a greater role in determining behaviour. However, the limitations of the factors review in terms of the type of data that was explored, as described above, could also suggest that illness representations did not appear in the review as this data was not explored, either through relevant surveys, such as the Illness Perception Questionnaire (Moss-Morris et al., 2002) or qualitatively. Other factors that are proposed to support self-regulation, such as self-efficacy and social influences were also evident from the review. The application of self-regulation theory to more general self-management behaviours in MS (Jopson and Moss-Morris, 2002) and the fact that it was not explicitly explored in the research that was reviewed would suggest that further, explicit, exploration of the theory, particularly illness representations warrants further investigation.

Congruence between the two areas of research

In line with other reviews that have tried to match adherence determinants and intervention targets (Allemann *et al.*, 2016; Johnston *et al.*, 2016) the findings from this review suggest that there is currently a lack of cohesion between these two areas of research. Research seeking to understand the correlates between patient features and adherence behaviours is producing many insights that are unmodifiable and inconsistent. Whilst these can help us understand *who* may benefit more from an intervention, they do not add to our knowledge of how to support change, or our understanding of the reasons behind these findings. In contrast, the majority of the successful behaviour change interventions provided one to one, exploratory and skills-based interventions, with some demonstrating an impact on both behavioural outcomes and proposed modifiable drivers of behaviour.

The paucity of data looking seeking to understand the patient perspective 'in their own words' has likely compounded the inconsistency of findings and limited the progression of our understanding. As proposed by Vermeire and colleagues (2001) and demonstrated by Pound *et al.*, (2005) much is to be gained in terms of our understanding if we seek to gather insights into medicine taking behaviour from the perspective of those prescribed the treatment in a qualitative way. Adherence is just a single, albeit important, aspect of chronic disease self-management and occurs as part of a fluctuating and individual experience of the condition. Data that tells us 'if someone is older they are more likely to be non-adherent' does little to shed any light on the complex, and individual, perceptual, cognitive and behavioural factors that are leading to a decision or ability to adhere.

Summary and implications for future research

This findings from this review suggest that our understanding of why people with MS are non-adherent requires a deeper and more complex exploration than has be attained by the work to date which has been largely reductive, quantitative and built on data that is pre-populated or convenient. The incongruence between research that explored the drivers of non-adherence and research that successfully targeted adherence related factors and positively influenced them, demonstrates that there is more to be understood about how these factors are working 'behaviourally' and their mechanisms of action.

The large range of factors found in the first part of the scoping review also suggests that this area of research in particular could benefit from a systematic review and / or meta-analysis of factors to help reduce the number of variables and prioritise future research.

The relative lack of qualitative study methods to explore adherence in MS to date, and the paucity of research building on theoretical models of behaviour in the first part of the review has likely contributed to the disconnect. It is proposed that a qualitative exploration will enhance our understanding, not only of the 'why' of correlations that have been previously found, but also help to elicit which aspects are susceptible to modification, thereby enhancing our ability to appropriately target interventions and, hopefully, increase their effectiveness.

Finally, the lack of findings relating to illness representations in particular suggest that this is also an area that has been underexplored and warrants further investigation.

Qualitative Research Study - Adherence in people with Multiple Sclerosis: perspectives of patients from Germany, Spain and the United Kingdom

Introduction

It was evident from the literature review conducted that there is a lack of qualitative research that has been conducted looking at the potential barriers to adherence in people with MS (PwMS). The majority of qualitative research in MS has explored other self-management behaviours, such exercise (Plow and Finlayson, 2014) and undertaking physiotherapy (Paul *et al.*, 2014); or it has been used to better understand the impact of living with the condition (Galushko *et al.*, 2014; Dennison *et al.*, 2011; Johnson *et al.*, 2004; Mohr *et al.*, 1999). Lowden and colleagues (2014) conducted a phenomenological study to better understand the patient experience of making a treatment decision, but this was focussed on initial choice, rather than adherence behaviours per se (Lowden, Lee and Ritchie, 2014).

Whilst the review conducted in the first part of this thesis provided some insight into potential drivers of nonadherence, as discussed, the design of the studies included meant that the majority of insights were generated from a-priori assumptions or limited to the extent of retrospective data available. Even the minority of studies that sought direct feedback from the patients did so through pre-defined survey responses. Some of the findings are supported further through their mapping onto the COM-B model of adherence, which in turn is supported by work relating to illness perceptions and treatment beliefs (motivational components) discussed in the review, however, the relationship between change to these factors and adherence outcomes was not statistically explored to determine the extent to which changing these factors mediated adherence outcomes. Furthermore, there were a large number of

factors that only appeared once or produced conflicting responses. A quantitative methodology will, to some extent, 'dismiss' these findings. However, as the frequency of response was often related to how often it was examined, it is possible that some of these factors are of greater importance than the research suggests.

The review also demonstrated that the majority of successful behaviour change interventions (albeit from a small sample) provided 'skills based' interventions, intended to support psychosocial as well as treatment factors that were modifiable. As per my review and the models utilised (SRM, COM-B, BCW), I wanted to further explore the idea that adherence is a part of an individual's overall coping strategy in terms of disease management (Leventhal *et al.*, 2016; Brandes and Mullan, 2014) and that, due to its multi-level nature, self-regulation will place adherence in the context of living with MS overall, rather than it being a discreet action. I also wanted to see the range of strategies and skills employed by people with MS to 'manage well' day to day and see how these aligned with behaviour change techniques identified from the review and / or suggested the value of additional support and intervention considerations.

I felt that this offered an opportunity to build on insights generated from the review, explore further the applicability of the identified models for this population and to expand on the body of research that has already explored self-management challenges in people with MS.

To this end I designed a qualitative study to explore the impact of perceptions and experiences on adherence in people with MS, within the context of

managing the condition overall. It is proposed that a qualitative exploration will help identify salient findings from the current body of research and allow for novel findings to be generated. In addition, the nature of exploratory research should allow for a greater understanding of the relationships and / or mechanisms of action between factors and behaviours through the provision of insights into the 'logic' of the participants.

Sponsorship

As well as contributing towards my Professional Doctorate, this piece of qualitative research was also used to support the design of a patient support programme for people prescribed two specific DMTs which would be sponsored by a pharmaceutical company. Therefore, this research was also sponsored by the company and they provided independent approval of the protocol and materials in line with European Healthcare Market Research Regulations (see ethical considerations and approvals section). This provided an opportunity to include participants from more than one country and utilise native speaking health psychology specialists in Germany and Spain. As well as embracing a broad sampling strategy it provided the opportunity to explore potential differences between / across cultures, which had also been lacking from the research found to date in my review.

Aims

The aims of this research were to:

- Understand the lived experience of MS and how it influences adherence.
- Explore illness and treatment perceptions of people with MS in line with key tenets of the self-regulatory model
- Investigate the drivers of and barriers to adherence and operationalise these utilising COM-B to compare to factors determined from the scoping review
- Explore potential differences between countries (Germany, Spain, & the UK)

Methodology

Design

Due to the exploratory nature of the research, a qualitative approach was chosen as opposed to a quantitative methodology. A qualitative approach allows the key issues to be explored in greater depth and offers a more flexible methodology, allowing for the research to adapt to findings and outcomes through the course of the study (Braun and Clarke, 2013). Whilst the research was 'top down' in that it was guided by an existing theoretical framework, namely the Self-Regulatory Model (SRM) (Leventhal *et al.*, 2016; Brandes and Mullan, 2014; Leventhal, Meyer and Nerenz, 1980) the relative paucity of qualitative data examining drivers of adherence in MS, means that there was justification in also seeking an opportunity to generate novel data, which would not be forthcoming from a purely quantitative data set (Braun and Clarke, 2013; Tolich and Davidson, 1999).

The aim of the qualitative research in this context was to gain detailed insights into the lived experience of healthcare and illness (Bishop and Yardley, 2007) and also the processes involved in health-related behaviours, in particular adherence to treatment. Therefore, a cross-sectional, semi-structured interview methodology was employed. This was to allow the research to be focussed on its primary aims without being too restrictive, giving the researcher an opportunity to explore and follow-up salient points. This meant that valuable new insights could be generated and the iterative development of the interview schedules to occur if applicable. This 'sequential analysis' allows for the exploration of 'interesting' data that are generated which are not included in the original research framework, thus increasing the potential richness of the data (Charmaz, 2002; Pope, Ziebland and Mays, 2000).

One-to-one interviews were chosen to allow for the detailed insights into individual perspectives and experiences to be obtained. In addition, as the topic of their illness is potentially sensitive and previous research indicated very individualised trajectories and experiences, it was believed that one-to-one interviews would encourage more open responses and allow for 'minority responses' that may not come out in a patient focus group (Bishop and Yardley, 2007).

Framework Analysis was selected to explore and analyse the data (Ritchie *et al.*, 2013). Framework analysis is a form of thematic analysis, lending itself to the exploration of experiences and factors influencing behaviour (Braun and Clarke, 2013). It is drawn from sociological research processes (Bloor, 1978) and has been widely used in an applied healthcare setting (Taylor-Robinson *et al.*, 2008; Ritchie and Spencer, 2002). Its 'systematic' nature lends itself to

answering questions related to healthcare system design and allows the analysis and findings to be viewed by audiences outside of academia (Ritchie and Spencer, 2002). Increasingly it has been used within health psychology to help understand experiences, illness representations and explore theoretical hypotheses (Bower *et al.*, 2012; Elliott, Fischer and Rennie, 1999) making it particularly relevant for this research. The method has also been used to explore reasons for non-adherence to medication in other patient groups (Thorneloe *et al.*, 2016; Lacey, Cate and Broadway, 2009). It was selected as, in line with the semi-structured interview approach to collect the data, it is both inductive and deductive in its approach, allowing analysis to be guided by explicit a priori aims (i.e., the SRM) as well as permitting concepts to be derived independently from the data (Pope, Ziebland and Mays, 2000). This is in contrast to methods such as Grounded Theory, or Interpretive Phenomenological Analysis (IPA) that are overwhelmingly inductive (Braun and Clarke, 2013). Neither was Discourse Analysis (DA) deemed appropriate as this would have provided insights into the language used by participants and how this shapes their reality but was unlikely to yield 'practical' insights relating to the overarching aims of the research (Braun and Clarke, 2013; Ritchie *et al.*, 2013). Finally, it was felt that this method was particularly useful for working across a data set that had been generated by a team of interviewers as the use of a matrix (participants in rows, themes / concepts in columns) helps to keep the data in context whilst still allowing for cross case and cross theme analysis (Ritchie *et al.*, 2013).

Participants

Purposeful sampling (Patton, 2014) was used to identify and recruit from across the three countries people with a diagnosis of MS, prescribed a DMT, who had a range of demographic and clinical characteristics (e.g. age, gender, levels of disability) and varied experiences relating to the objectives of the research (e.g. time since diagnosis, symptom experience) to help make the research as inclusive as possible and to explore potential temporal effects of both disease and treatment.

This sample size was selected in line with recommendations relating to the type of research question (experience / influencing factors), the data collection method (interviews) and analysis method (thematic analysis; framework). In relation to this combination of factors it is recommended that a sample size of 6-10 is sufficient to be able to capture a range of perspectives (Braun and Clarke, 2013). Eight participants were sought for each country. This was to allow for both country specific data to be compared as discrete sets whilst still having a 'manageable' whole data set (n=24).

Methods

Recruitment strategy and procedure

Patients were recruited through specialised market research agencies in each country utilising their MS research panel members. I provided multiple agencies with the sample criteria and a top-level overview of the research protocol to enable them to furnish me with quotes and timeframes for recruitment. Three agencies were selected (1 per country) based on cost and time to recruit.

I created the necessary recruitment documentation in English (screening questionnaire, patient confirmation email / letter, research information sheet

and consent form – see appendix iii) and these were then translated into German and Spanish by the German and Spanish health psychologists working on the project. These documents were supplied to the chosen recruitment agencies in each country.

Agencies performed the initial screening, utilising existing research panel members and performing pro-active recruitment where required to meet sample requirements. Once suitable participants were identified, the agency was tasked with sending the patient a confirmation email or letter which also included a copy of the research information sheet and consent form. The agency was tasked with collecting initial consent to take part. Once the participants returned the consent forms, the agency liaised with them, myself and the other two interviewers to determine suitable times for the interview to take place. Contact details were provided to me and the German and Spanish interviewers which included the participant's name and telephone number. As project lead, I was forwarded all the consent forms for audit purposes.

The other interviewers and I called participants at the agreed time. If the participant responded, we would check that it was still an appropriate time and either proceed, rearrange or terminate as appropriate. If proceeding, the interviewer would check understanding of the research and reiterate the components of the consent, namely sponsorship, data privacy and the right to withdraw at any point. Verbal consent was also taken to record the conversation. If there was no response, the interviewer would try a maximum of three times in the 15-minute period directly following the arranged time of the call. If there was still no response, the interviewer would notify the market research agency for them to manage the rearrangement of the interview.

Participants were remunerated £50 / €50 dependent on country in line with European Healthcare Market Research regulations and this was handled by the recruitment agency.

Ethical considerations and approval

Within the pharmaceutical industry, patient qualitative research falls under the auspices of the European Pharmaceutical Marketing Research Association (EphMRA) in relation to the appropriateness of the research itself and the European Medicines Agency (EMA) with regards to the reporting of adverse events. Pharmaceutical companies will use the guidance from these regulatory bodies to inform their own approval processes. The procedure undertaken for this study is outline below.

Study and materials review and approval

The research protocol and interview guide were all approved via a system called 'Zinc Maps'. Zinc Maps is a web-based application designed to accommodate materials requiring multi-stakeholder approval. It is used comprehensively in the pharmaceutical industry and provides a repository for any materials that require approval and a chain of evidence of who has approved what, when. For the purpose of this research the sponsoring company are the owners of the Zinc process and all the materials within. I was the person who had overall responsibility for the origination of all the English versions of the documents, research design etc. and ensuring that the research project was conducted in line with the approved protocol.

In this instance the research protocol and interview guide were reviewed and approved firstly at a regional level, to ensure consistency and applicability with

European Healthcare Market Research regulations. Materials (e.g. interview guide, consent forms etc.) were then approved at a local level where required to ensure consistency and applicability with UK / German / Spanish pharmaceutical market research regulations as appropriate. This differed between countries as the regional approval was sufficient to cover the research in all countries, but some markets required / chose to go through a process of local approval as well.

Roles that would have been involved in review and approval include; legal, regulatory, medical and pharmacovigilance teams – these teams operate separately to the patient services team who sponsored the research. In this way the Zinc process can be seen as the equivalent of an ‘independent’ review panel within the pharmaceutical company, as you would have within a University structure.

The following is a list of the approved documents by country. Approved versions are in the appendices and the approval stamp is either on the first page of the document and / or in the footer.

[Research protocol](#)

This was reviewed and approved at a regional level (as evidenced by the EMEA (Europe, Middle East and Asia) stamp) because the regional patient services team were the primary sponsors of the research overall. This is available for review in appendix iv.

[Research interview guides](#)

- Spanish and German versions were informally reviewed at a local level but these markets chose to cascade from the EMEA level formal

approval (*EMEA MS Research Interview Guide, appendix v*) as there were no significant changes made.

- The UK did an additional formal local approval of the regional version (*UK MS Research Interview Guide, appendix vi*), as evidenced by the additional footer with a UK reference, this was because they used a different (local) SOP (standard operating procedure) for adverse event reporting

Supporting research materials

- Only the UK opted for formal Zinc approval of the additional research materials (*UK MS Research Supporting Materials appendix iii*) – this is evidenced by the footer with a UK reference.

Minor amends were made based on specific regulations (e.g. Spain could not collect data on medicine history, only current treatments, whereas England and Germany could) but it was felt that none of these amends changed the study conditions such that they would have a detrimental impact on the study or unduly influence the findings.

University of the West of England (UWE) ethics approval

Evidence of the independent approval of this research (as outlined above) was supplied to the UWE ethics board as they did not review a proposal for this research before it was undertaken. This was following a request from the examiners during the viva for this thesis submission, and to ensure that the review board were satisfied with the approval process that had occurred and that the research was suitable for inclusion in the UWE research repository. The Chair of HAS Faculty Research Ethics committee (FREC) reviewed the process and the supporting materials (appendices iii – vi). She stated that they

were not able to provide retrospective approval as it should have gone through the formal FREC system but that there was clear evidence of review and that ethical principles had been adhered to. A copy of this email is included as appendix vii. Under advisement of the graduate school and my supervisor I proceeded with this submission on the basis of this feedback.

Informed consent

As described in the procedures above, participants were required to give informed consent prior to taking part in this research; it was obtained in writing prior to the interview and confirmed again verbally over the telephone before commencing the interview questions. Participants received a consent form and information sheet alongside their formal research invitation (email or hard copy letter). The information sheet outlined the aims and procedures of the research, the type of information to be collected and to outline confidentiality and data protection procedures. They were informed that participation was completely voluntary and that they had the right to withdraw at any time without giving a reason or justification. They were also provided contact details (of the recruitment agency) in the event of any questions prior to or after the research interviews.

Calls were not scheduled until a signed consent was received (either by post, fax, or email scanned copy). At the start of each telephone call the researcher reiterated the important, salient information as described above, including specific examples, and gave the participant opportunity to ask questions.

The ability to give informed consent requires a sufficient level of mental and cognitive ability in order to understand what is involved in the research. Whilst MS can impair cognitive functioning, as a whole, the population are not

considered mentally impaired by proxy of having MS. The recruitment agency, who are specialists in recruiting patients with chronic illness for the purposes of research, had the initial responsibility to screen out individuals who had impairments in understanding or communication that might affect their ability to give informed consent or sufficiently engage with the research process (e.g. patients with severe or profound intellectual disability or some people experiencing mental illness). However, each interviewer was also responsible for checking an individual's ability to give informed consent at the start of each interview.

It is worth noting at this stage that, within the remit of the guidance, research such as this can be blinded to participants and this is often preferable to reduce the likelihood of research being seen as promotion of the company or inducement to seek out a particular treatment. Guidance states that it should be made clear that research is being supported by a pharmaceutical company but not which one. However, if a participant asks to know the identity of the company then it must be disclosed and if an adverse event is reported then the company will also be declared as this information will need to be shared directly with them (EphMRA, 2016). To this end, this research was blinded in this way and the company only revealed during adverse event data capture or if asked directly by a participant.

Participant confidentiality and data protection

Different parties involved had knowledge of the identity of the participants commensurate but limited to what was required to perform their roles within the research. The recruitment agency held the most personal identifiable data as they were responsible for contacting and sharing materials and reimbursement with participants, to this end they had email / telephone /

address details as well as names. The Spanish and German interviewers and I were provided with first names and contact telephone numbers only in order to be able to conduct the interviews. I received copies of all the signed consent forms which contained participants full names and signatures.

During the data collection, each participant was allocated a unique participant ID number which correspond to computer files, audio recordings and transcripts. This coding system was used when sending audio files for transcription and translation meaning that the transcription company only had names as per the audio recording. As part of the transcription service participant names were then removed from the transcripts themselves as they were not required to perform analysis.

Electronic interview transcripts were all sent to the relevant local Atlantis Healthcare offices for initial quality review by the relevant person who conducted the interviews. Translated transcripts (into English from German and Spanish) were then electronically shared with myself for analysis. Any hard copy materials were kept in a locked cupboard in a lockable room accessible by the research team only. Electronic data and audio recordings were kept on a secure server in password protected files. All data will be kept for 10 years in accordance with the Data Protection Act (1998) and is subject to regulatory audit.

In the case of adverse event reporting (see separate section), participants were specifically asked if they would like to waive their anonymity.

Data has been reported in an aggregated form to protect anonymity and confidentiality. Where direct quotes are used, information that could be deemed identifiable (e.g. names, specific locations) has been removed.

Potential risk to participants

The overall risk to people participating in this research study was considered to be low. The likelihood of physical risk was very low as there were no tasks or physical requirements to the research. Participants were however asked for demographic information (age, gender) and self-reported social and emotional wellbeing with particular reference to their condition. These questions may be perceived as sensitive to some people and could evoke an emotional reaction. For this reason, there was a small likelihood of psychological risk as a result of reflecting on their condition and overall well-being. To this end, participants were advised at the end of each interview that, if they were experiencing any 'adverse' feelings following the interview that they may want to consider talking to someone appropriate. The guidance included in the interview scripts was as follows:

Just before we go, I wanted to say that we understand it can be quite tiring to talk about these types of things in depth, so don't be surprised if you feel a little tired, or you find yourself thinking about some of the things that we have talked about. If you do feel as if you would like to talk about anything that we have discussed more, it can be a good idea to talk to someone with some expertise in this area – perhaps your GP or a member of the team at your hospital / clinic

No one reported any adverse psychological effects from the interviews to the interviewers or recruitment teams.

Adverse event training and reporting

Pharmacovigilance refers to the science and activities that support detection, understanding, assessment and prevention of adverse effects or any other medicine related problem. The European Medicines Agency (EMA) coordinates the European Union (EU) pharmacovigilance system and supporting services and processes to support this system. As evidence for medicines safety is limited to clinical trial populations prior to authorisation, it is deemed essential that the safety of all medicines continues to be monitored throughout its use in healthcare practice (EMA, 2016). To this end, as this research was sponsored by a pharmaceutical agency and it was possible that people involved were currently or previously prescribed medicines produced by the sponsoring company, it was necessary for the research team to undertake adverse event training provided by the pharmaceutical company and to record and report any adverse events in accordance with the company's adverse event reporting adverse event reporting standard operating procedure (SOP). A copy of the SOP is not available as the sponsoring company would not agree for this to be shared but the text used in the event of needing to report an adverse event is included in the approved protocol (appendix iv).

Materials and equipment

Interview schedule

The interview schedule was based on the key aims of the research outlined above, drawing on the SRM framework. As with the recruitment material, I created the master interview schedule in English for subsequent translation. To meet the research objectives, I felt it was important to get the balance between deductive and inductive questioning. As seen in the review I undertook and as posited by other researchers (Pound *et al.*, 2005; Vermeire *et al.*, 2001) deductive methods have done little to enhance our understanding in terms of the most salient and modifiable drivers of adherence behaviour. However, this does not mean previous research is not of value, and that theories and models which have shown relevance in other areas will not apply to people with MS. Therefore, I designed the research questions and prompts to help gain both a deeper understanding of what is already hypothesised and what 'holds true' as well as giving opportunity for people with MS to provide novel insights and perspectives. The Illness Perception Questionnaire is a common method of operationalising the mental representations of the self-regulatory model (Jopson and Moss-Morris, 2003; Moss-Morris *et al.*, 2002) and I used this as a basis for creating the questions and prompts to explore beliefs related to the *cause* of the illness, its *nature* or identity, its *duration*, the personal *consequences* of suffering from it and the extent to which the illness can be *controlled* or cured (Broadbent *et al.*, 2006; Leventhal, Meyer and Nerenz, 1980). In addition, as a recent review has demonstrated the utility of the Necessity-Concerns framework to determine adherence behaviours across condition and its 'natural' extension of the SRM, questions were included to explore beliefs related to treatment necessity and concerns, as

outlined by in the Beliefs about Medicines Questionnaire (Horne, Weinman and Hankins, 1999).

As previously indicated, I wanted to ensure that there was also opportunity for novel data to be put forward by the participants, this necessitated the use of open questions and prompts, rather than closed, survey-based interviews which are the key features of much of the research done previously in this area. This meant that the structure and aims became a starting point for discussion, rather than a restriction. The structure of the schedule followed a pattern of broad starting questions (sometimes referred to as “leading-in” (Arthur and Nazroo, 2003)) to put the interviewee at ease and to start to focus attention towards their experiences of MS, followed by narrower, more specific topics to help meet the research objectives and completing with a broad “leading-out” question to provide an opportunity for the participant to talk about any related issues not yet covered or remembered after the fact (Kvale and Brinkman, 2009; Arthur and Nazroo, 2003).

The key topics of the schedule and a brief rationale for their inclusion are listed below; a copy of the full schedule is available (see appendix v).

Broad - Leading in

- Experience with MS
 - Diagnosis, day to day impact, symptoms, future, control, understanding *[draws on key questions and domains of the IPQ]*
- Experience with treatment
 - Understanding, efficacy, control, necessity, concerns, side effects, types *[draws on key questions and domains of the IPQ and the BMQ, as well as exploring potential differences between treatment types as was found in the review]*

Specific

- Levels of adherence and persistence (current, prior) *[to compare and understand perceptions and general self-management strategies between people with differing levels of adherence and to try to get to the 'why' of the differences in behavioural outcomes]*
- Medicine management / regimen *[to investigate the findings from the review regarding treatment type and the impact on adherence]*
- Self-efficacy to manage treatment *[to investigate the findings from the review that self-efficacy is an important driver to adherence and to understand what helps people with MS to feel confident about managing their condition and treatment]*
- Reasons for adherence / non-adherence / treatment changes *[to build on the current research by providing an opportunity to patients to*

describe in their own words the 'logic' behind their treatment-based decisions]

- Self-management strategies - living day to day with MS *[to investigate how adherence fits in with general coping strategies].*
- Therapeutic relationship with HCP *[Many of the interventions did offer a form of therapeutic relationship, so I wanted to see how important this was for people with MS and how it impacted their behaviours]*
- Social support *[To explore the relevance of this to self-management in line with COM-B]*

Broad - Leading out

- Thinking about the things we have discussed, is there anything else that you think is important to consider?

Suitability and evolution of the interview guide

Guidance for qualitative research suggests that, where possible, interview guides are piloted to test its suitability and efficacy (e.g. is it garnering the type of data you expect, do people seem able / willing to answer the questions) (Braun and Clarke, 2013). However, it is acknowledged that in many cases, formal piloting is not practical or possible, which was the case with this research. To this end, they recommend reviewing the guide after the first few interviews to determine if any changes do need to be made (Braun and Clarke, 2013).

I arranged for the interview guide to be reviewed after one interview had been conducted in each country to assess the suitability of the schedule in terms of content, relevance, clarity, tone and length and to uncover any country specific considerations or general amends that were needed. Following this discussion it was evident that there were no country specific differences required and the overall schedule was fit for purpose. However, it was apparent that some of the prompts required a more positive framing to try to elicit good experiences as well as struggles. For example, we decided that prompts such as *“What was your experience of being told you had multiple sclerosis?”* and *“Tell me about your treatment experience with MS?”* would benefit from having an associated follow-on prompt of *“Can you describe if there was anything positive that came from these experiences”* where responses were felt to be negatively focused. Similarly, for the question *“Would you feel comfortable talking to your HCP about problems or concerns you had relating to your treatment?”* we felt it was important to consider a follow-on prompt relating to discussing positive treatment experiences with their HCP. These additional prompts did not change the overall structure of the guide or impact any of the leading questions, therefore formal amendments to, and re-approval of the guide were not required.

Furthermore, as the schedule was intended to be a guide, rather than to be completed verbatim, all interviewers were able to make minor additions and amends throughout the process of interviews to reflect growing understand of the population and to ‘test’ novel data that was being generated, in line with the tenets of an iterative, qualitative research process (Charmaz, 2002). For example, as I began to notice people talking about how guilty they felt in relation to needing the support of friends and family, or having to prioritise

their needs over others, I would then explore in subsequent interviews how people felt about asking for or receiving support when they stated that this was something which happened. Again, these did not result in formal amendments to the guides but were considered a ‘natural’ part of the process to be acknowledged. Figure 6 shows the timeline for the data collection phase of this research.

Figure 6 – Timeline for data collection and review of interview guide

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
First interviews								
Review meeting and minor amends								
Remaining interviews								

Recording, transcription and translation

All interviews were conducted via an in-house telephone system that automatically records all calls. The recordings were extracted as individual audio files, based on time of call and phone extension used. Each interview lasted between 40 and 60 minutes. Direct transcriptions of each audio file were made by an external transcription service based in the US, with the German and Spanish transcripts also being translated into English by the same agency. All transcripts were returned to the respective interviewers (German and Spanish interviewers were also fluent in English) to check a sample for consistency against recordings. They were then all sent to me as the research lead for analysis.

Data were analysed using NVivo 10 Pro for Windows (QSR International).

Analysis

Framework Analysis

Framework analysis is built around the tenet of what Bloor describes as 'Analytic Induction' (Bloor, 1978). This is whereby hypotheses are derived from a set of cases and further cases are then used to continue to test this as appropriate.

Process of analysis

Ritchie and colleagues (2013) describe 5 stages to Framework analysis: familiarisation; identification / creation of a framework; indexing; charting summaries; and mapping / interpretation. These, as well as general recommendations for thematic analysis (Braun and Clarke, 2013; Braun and Clarke, 2006) were used as guidance for the data analysis.

Familiarisation

The aim of this first stage, familiarisation, is to get to know the data, both in terms of the individual interviews themselves and also the overall 'sense' from the data, often referred to as immersion and is a key starting point for many types of qualitative research (Braun and Clarke, 2013; Ritchie *et al.*, 2013). To do this, I read all the transcripts on average between 3-5 times at this stage (depending on the depth of detail within the scripts and my prior level of familiarisation, for example interviews I had conducted myself versus German and Spanish ones). I made notes on key observations, in terms of things that were 'interesting', both from individual transcripts but also across the data set. Braun and Clarke (2013) refer to these observations as 'noticings'. Some initial noticings included an apparent dichotomy between people who had

adjusted reasonably well and those who were struggling (or had struggled in the past), and the differences between the attitudes and experiences. For example, level of focus on the condition, support network and social experiences. The different manifestations of guilt, which remained a discreet theme until the end of the analysis, were particularly apparent at this stage as well, though not the extent to which it could be mechanism for action.

Framework development, indexing / coding and summaries of cases

As this was a qualitative study that was based on a theoretical underpinning, the starting framework was based on the key sections of interview schedule, as these represented key tenets of the theoretical models and findings from the review that were being explored further. Potential additional categories from the familiarisation phase were also added initially. On the whole these were sub-components of interview schedule categories, for example splitting MS Experiences into diagnosis / early stages and current / on-going. It was then an iterative process between indexing and coding the transcripts into NVivo as participant cases according to the framework but also allowing for any additional categories that did not have a 'home'.

The final overarching categories were:

- MS Experience – Diagnosis / Early Stages
- MS Experience – Current / On-going
- MS Experience – Future
- Illness Perceptions
- Treatment Experience – Past
- Treatment Experience – Current
- Treatment Beliefs and Comprehension

- Adherence – Extent of
- Adherence – Drivers of
- Self-efficacy
- Self-management
- Experiences with healthcare system / teams
- Social support – managing disease / treatment
- Social experiences (e.g. stigma, work)

There was also a placeholder of 'other' for sections of the script that did not fit, primarily consisting of interactions between the interviewer and the interviewee that were 'outside' of the core topics. However, this category was still reviewed during the coding phase to ensure there were no topics / themes or influencing factors that would not have been included in the main framework categories.

At this stage, some transcript sections would appear in multiple categories, in particular where sections highlighted the links between categories – such as drivers of adherence and illness perceptions, or self-management and level social support.

During the indexing process, data were coded both semantically (e.g. the explicit content of the data) and then latent codes were applied (e.g. the implicit meaning from the data derived from a theoretical concept, such as illness identity, and / or my own concept of the data). This allowed for knowledge to be gained from the explicit data to help understand the overt relationships between beliefs, experiences and behaviours and also for the data to be synthesised and interpreted as a total dataset to test and produce population level hypotheses. Indexing at this stage also included the creation of supporting descriptions of how the data informed a category or case level summary. Data coding

examples (extracted from NVivo into Excel) from the overarching framework are in appendix viii.

Once this coding had been completed, I explored the data again according to the framework structure and by individual codes. This part of the process helped me to create the 'story' of each element by looking at these sections as cases in their own right and testing the concepts *across* the data. Two examples of this are in appendix ix.

Interpretation

This stage represented the opportunity to take the 'top down' data as provided by the framework, and to move beyond managing it to understanding it as a whole data set (Ritchie *et al.*, 2013). At this stage, latent coding in particular proved to be a key reference point to 'bringing' out the key themes that underpinned a number of the semantic categories. Alignment between categories and subsequent coding supporting the identification of relationships between people's experiences / perceptions and their behaviours. For example, guilt (which had been a 'noticing' from the familiarisation stage) was woven through a number of categories, including: MS Experience – Future; Adherence – Drivers of; Self-Management and Social Support. When reviewing independent codes of guilt, it was possible to see that not only was this something that people felt, but that it was also a source a conflict. Between what people wanted now versus implications for the future or needing support from family but not wanting to be a burden. In this way, although the research had been built on a priori assumptions, novel themes were identified. These were finally built into a model with overarching themes, themes and sub-themes (Braun and Clarke, 2013) and how they appear to link into each other.

Quality of the analysis

There is much discussion relating to the applicability of quantitative quality criteria to qualitative research (Braun and Clarke, 2013; Yardley, 2008). For example, the tenet of data reliability and its ability to be generalised irrespective of the 'researcher' and the specific members of a participant group speaks to a hypothesis that there is one version of the truth and that the researcher and research process should have a minimal impact on that truth. This is at odds with principles of qualitative research which fully acknowledge the role of the researcher in the process, from their skills at eliciting data from people through interview and focus group techniques to how their own standpoint and experience influences the interpretation and categorisation of the data. Furthermore, qualitative approaches acknowledge the 'context bound nature of reality' (Braun and Clarke, 2013, pg. 279) and that therefore there is no single perspective that can apply to all.

In this research study, data were collected by three different researchers but analysed only by me. Whilst the clarification and input of the other interviewers was sought, this was principally to ensure that their own experiences from the research process were not literally 'lost in translation' and to seek their understanding, or clarification of the data they collected. This was not an attempt at inter-rater reliability whereby the test is "do all researchers reach an objective agreement" as it was felt that this was neither necessary nor valuable. As described in an empirical study conducted by a group of researchers looking at the role of inter-rater reliability in qualitative research, separate analysis of the same data produced close agreement on the basic themes, but they were all 'packaged' differently, dependent on the different researchers own experiences and points of view (Armstrong *et al.*,

1997). To this end, it can be posited that the 'reliability' comes from the following and description of a dependable set of methods to collect and analyse the data, whilst being open, and to some extent even embracing, the context the researcher themselves brings (Braun and Clarke, 2013; Yardley, 2003).

This leads into the concept of transparency, which is highlighted by a number of guidelines as an indicator of good practice (Malterud, 2001; Yardley, 2000). As well as a clear description of the methods, quotations from the original text have been used as exemplars to support the integrity of interpretations and to help demonstrate the link between the raw data and the findings (Elliott, Fischer and Rennie, 1999).

It is acknowledged that there is an increased risk of misinterpretation of the data with the translated manuscripts, particularly as I had not conducted this set of interviews but did undertake the analysis. However, as described above, processes were put in place to try to mitigate this risk as much as possible. This included a review of translated transcripts by the relevant interviewers to check translation quality and the check in and clarification actions that I undertook throughout the analysis process.

During different stages of this analysis process I sought clarification and feedback from the other interviewers involved in the research. This took place after the initial framework creation, following the indexing and restructuring of the data and at the end of the process. Individual clarification was also sought as and when required in relation to parts of transcripts that had been conducted in Germany and Spain.

Results

Sample

A total of twenty-four eligible PwMS were recruited and interviewed across three countries; UK, Germany and Spain, with eight participants from each country. A total of twelve males and twelve females participated. All participants were diagnosed with Relapse-Remitting MS (RRMS), all had been diagnosed more than two years prior to taking part in the research with the exception of one participant in the UK, who had been diagnosed less than two years prior and all were currently prescribed a treatment for MS. Disability was assessed through patient self-report at screening using criteria based on levels of symptoms and disability impact, adapted from the Expanded Disability Status Scale (EDSS, Kurtzke, 1983). Further details of the sample are available in Table 9.

Table 9 – Demographic details of participants by country

Country	Gender	Age Range	Current Treatment	No. of previous treatments	Level of MS Related Disability
Germany (<i>n</i> =8)	Female <i>n</i> =4	30–59 yrs	Avonex <i>n</i> =1 Betaferon <i>n</i> =3 Copaxone <i>n</i> =1 Gilenya <i>n</i> =2 Tysabri <i>n</i> =1	0 <i>n</i> =4 1 <i>n</i> =2 3 <i>n</i> =1 4 <i>n</i> =1	Mild Disability <i>n</i> =4 Moderate Disability <i>n</i> =3 Severe Disability <i>n</i> =1
Spain (<i>n</i> =8)	Female <i>n</i> =2	25–54 yrs	Avonex <i>n</i> =1 Betaferon <i>n</i> =3 Copaxone <i>n</i> =1 Gilenya <i>n</i> =2 Rebif <i>n</i> =2	0 <i>n</i> =3 1 <i>n</i> =2 2 <i>n</i> =2 5 <i>n</i> =1	No symptoms <i>n</i> =1 Some symptoms, no disability <i>n</i> =4 Mild Disability <i>n</i> =2 Severe <i>n</i> =1
UK (<i>n</i> =8)	Female <i>n</i> =6	30–50 yrs	Alemtuzumab <i>n</i> =1 Betaferon <i>n</i> =1 Copaxone <i>n</i> =4 Tysabri <i>n</i> =2	0 <i>n</i> =2 1 <i>n</i> =5 2 <i>n</i> =1	Some symptoms, no disability <i>n</i> =2 Mild Disability <i>n</i> =2 Moderate Disability <i>n</i> =4

Themes

Initially, results are presented as per the thematic structure that was created through the framework analysis process, to support the aim to allow for novel ideas to be presented.

Subsequently, to build on the work done through the scoping review and to establish how these findings support / enhance or refute hypothesised models, findings will then be discussed as in relation to the aims of the research and operationalised using the COM-B framework.

Themes were consistent across the 3 countries and are therefore presented with supporting evidence from all 3 sets of interviews. Quotes are coded by country.

In line with recommended methods for organising themes in data (Braun and Clarke, 2013) they are presented as follows:

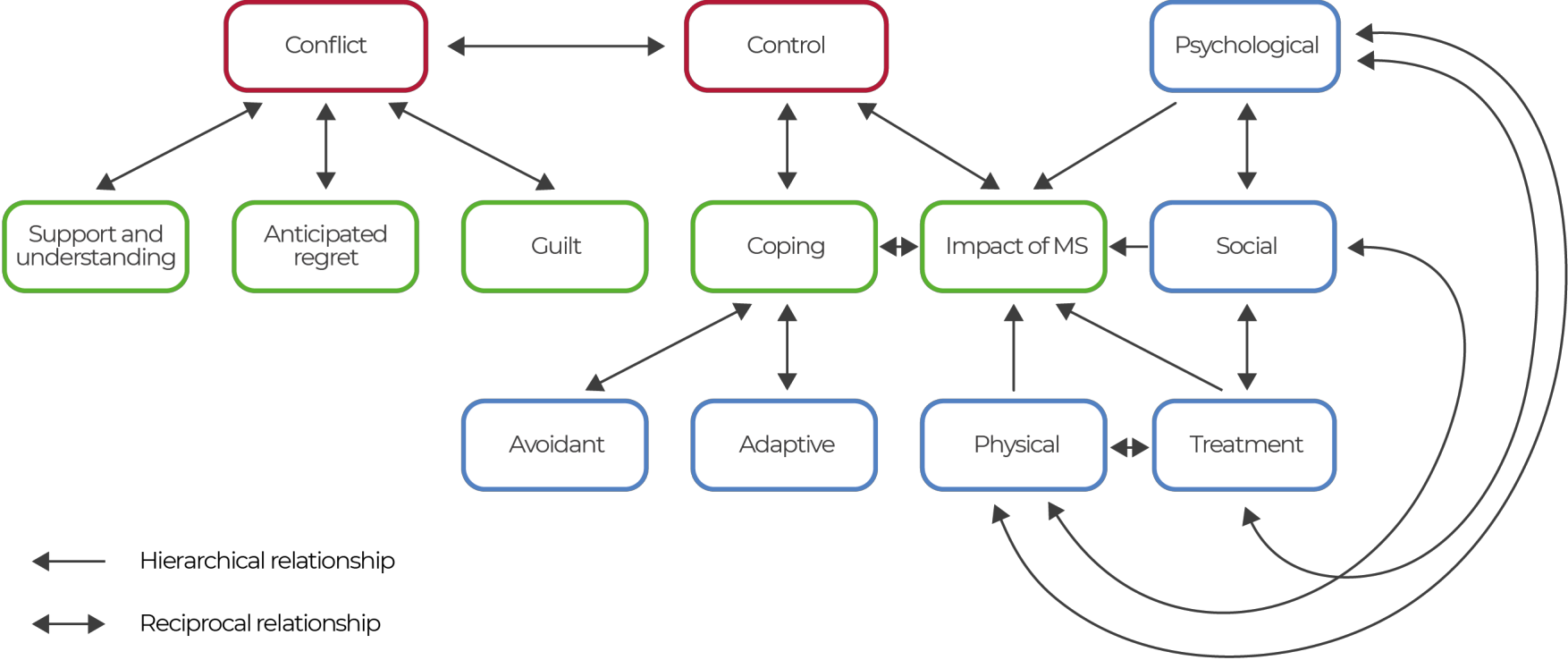
Overarching Themes – These are themes which encapsulate a common idea presented in the main themes from the data, but do not contain discrete examples.

Themes – These are the key patterns of data, related to the key objectives of the research, which inform our understanding of the data and provide the evidence for the overarching themes.

Subthemes – These represent, where relevant, specific concepts that may make up part of a broader theme.

Themes are visually represented in Figure 7.

Figure 7: Model of Thematic Relationships



Overarching Theme: Control

Control was an overarching theme that had a bi-directional feed with many of the themes that were derived from the data set, including the second overarching theme, conflict. The need to feel in control was often a positive driver of self-management behaviours, including adherence, as a way of coping. These coping strategies were employed in order to gain a sense of control over their MS, though for some there was a degree of fatalistic acceptance that MS was in control of them; they simply had to manage as best they could with whatever MS decided to 'give them'. The 'battle' between whether it was them or the condition that was in control linked into the conflict theme. In addition, whilst people realised MS was something that was largely genetic, many people still used language to refer to it as 'other', reinforcing the notion of conflict between what they could do and what the disease had power (control) over. Using coping strategies to reduce the impact of MS was a key way to feel in control. This was not just in response to symptom experience but also as a preventative measure, whereby not feeling or being in control was detrimental to their condition. For example, not controlling or minimising stress was seen as a key risk for relapses. To this end, control appeared to be an overarching theme as not only does it drive self-management behaviours, but the reciprocal nature of the relationship means that feeling in control is an important state for many people, which can be felt through the execution of coping strategies and / or through changes to the perceived impact of MS.

Theme: Impact of MS - "I am at the mercy of it"

The impact of living with MS was different for different people, driven by a number of factors that could be categorised into four key sub-themes; physical (e.g. symptom experience, disability), psychological (e.g. stress, anger), social (e.g. reduced ability to work, isolation) and treatment (e.g. injection burden, side effects). Whilst all could independently influence perceptions of impact, they were interrelated with each other as well. For example, physical symptoms limiting social activities, social limitations having negative psychological consequences and psychological burden reducing ability to self-manage. As described above, the interplay between the impact of the condition and the success of coping strategies was both driven by and influential on people's sense of control.

Sub-theme: Physical Impact

"Today we'll pick on her, today we'll give her a pain here, we'll give her a pain there."

(UK)

Across the sample, people experienced different levels of physical and cognitive symptoms as a result of their MS.

"Right now, the truth is that I do not notice symptoms as such.... you're more tired and such but I've always been clumsy" (ESP)

"All of a sudden my eyesight has gone funny and I have these blind spots all of a sudden and it is completely out of control. I have no say in it and I am at the mercy of it, really." (UK)

Physical symptoms were catalysts for diagnosis, acknowledgement of the disease and self-management behaviours, including taking treatment.

“Through the medication I can [control MS], I would say, because the medication I am currently taking, since I use this medicine, I must say, it's so good to me, how I was with still no other medication.” (DE)

“...it (being diagnosed with MS) didn't really mean, it didn't mean anything to me until it really started affecting how I felt.” (UK)

Conversely, whilst the absence or relative mildness of symptoms could cause people to doubt the need for treatment or even the validity of their illness, in this sample people still largely persisted with treatment regardless, due to fear about what ‘might’ happen in the future (see Anticipated Regret) but also to help maintain a sense of control in the here and now.

“Sometimes I feel like I am on this medicine and I don't know why I am on it...obviously I understand that, you know, I have got these changes in my MRI but because I am well, in myself, sometimes I feel like a bit of a fraud” (UK)

“It never goes away, it is a worry and it affects everything, whereas when you are taking medication it pushes it more to the back of your mind. It is there but it is not taking over your mind” (UK)

Though there was also evidence of symptoms being a physical prompt for medicine taking behaviour, not just a motivational driver.

*“Possibly it’s been a good day and (I) forgot about it” (taking treatment)
(UK)*

Cognitive and physical symptoms could also be barriers to people executing self-management behaviours, such as making it difficult to remember to take medicine or actually administer injections.

“I’m one of these anyway with short memory loss so I have to write everything down... so it’s not something I should forget but I have forgotten it in the past...” (UK)

“... because one day, then logically you forget because you’re doing - you’ve come home late, you forgot because you get very tired...” (ESP)

“And also if my hands aren’t working very well...someone else had to do the injection.” (UK)

People would mitigate these challenges through asking for support from others and trying to incorporate taking treatment with daily routines.

“...three times when I’ve missed it in the last six years or whatever it is, and that’s when I haven’t had the routine” (UK)

“Because I have lots of medication that I take during the day, so he is always texting and things, saying have you taken your tablets and stuff.” (UK)

As well as impacting self-management, the experience of physical symptoms could also influence psychological wellbeing and social factors, such as ability to work or go places.

“Now I'm just low, precisely because, by reason of the pain and the view that working in front of a computer I get a lot of trouble and pain naturally.” (ESP)

“...it was my bladder and I found that a nightmare because it would cause me a lot of anxiety about leaving the house” (UK)

Sub-theme: Social Impact

“People get a little frightened” (UK)

As described in the section on physical symptoms, many people were significantly impacted socially by MS, often congruent with symptom experience and level of disability. Reduced ability to work and take part in social activities were prolific examples.

“I am not going back to teaching. I would like to do something, but my husband said the stress, he couldn't cope with the worry, as if I get stressed I will need the wheelchair again.” (UK)

“So I think that is why, when I see friends going off and doing, you know, horse riding at the weekend or, you know, going for walks and things and I think I used to do all long walks and I can't do that anymore.” (UK)

In addition to the 'physical' restrictions, people would feel socially isolated from friends and family when they felt that their condition or experiences were not understood.

"...because you lose a lot of friends if you have MS. People get a little frightened" (UK)

"...people with multiple sclerosis, at a time when they run out of friends. Typically, they are, those who are married, then usually end up separating. I mean this, this breaks your life...I think it is by laying, fear, ignorance of those around you" (ESP)

However, where support was positive from friends, family and healthcare professionals this could be beneficial, such as practical support with managing treatment as described above, but also emotionally (see theme 'Support and Understanding'). A desire to maintain social and familial relationships was a driver of self-management.

"Basically, I've got a five-year-old girl so it's something I just have to get on and live with. I rest as much as I can". (UK)

Social experiences in terms of exposure to others with MS was sometimes beneficial and sometimes not. For example, two participants both had family members who had MS, for one this was reassuring as the impact on their lives (to date) had been minimal, for another the experience of her mother's disease course caused her to try to avoid fully acknowledging what was happening and impacted her initial reaction when she finally received her 'formal' diagnosis.

“Yeah, because my mum had MS but she had it really badly. She was quite severely affected by it. I started getting symptoms in the last year of her life. She had MS for years and years and I just couldn't bear to tell my family so I just buried it and kept it to myself for about four years but I knew what these symptoms were...when I was diagnosed I almost went into shock and for the first year I felt like I was just floating around”
(UK)

“I was kind of put at ease when I was explained more about it and looked it up a wee bit and, I think by talking to people and keeping a positive attitude...my Dad's two - brother and sister they are - his first cousins have got it as well, and they've had it over 25 years and they're still - touch wood - alive and kicking and well. So, I've known through them”
(UK)

Sub-theme: Psychological Impact

“I felt very sad ... very very sad” (ESP)

Most people experienced a degree of psychological impact as a result of their MS. The extent to which this impacted people was variable across the group. For example, some people experienced quite severe psychological problems that required treatment.

“I went to the doctor, a neurologist, which asked him to send me to a psychologist because I felt very sad ... very very sad and actually, I was diagnosed that I have a small depression” (ESP)

“I got severe problems with my psyche, because I couldn’t cope with the disease and with the associated problems... I searched for psychological support, because I couldn’t stand the situation anymore...”

Some people also felt that the relationship was two-way and that their psychological state could have an impact on their MS, with a perception that the ability to control their emotions, in particular stress, could lead to greater control over the condition.

“And when you are first diagnosed, because of the psychological impact of the diagnosis you start thinking: maybe that is why I am having these relapses.” (UK)

“I do not think that I have really control, however I do believe that I still, if I pay attention to me, I’m doing something good, try to avoid stress...can exert influence on it” (DE)

For many, the psychological impact varied over the course of their condition. For some diagnosis was a particularly difficult time.

“And then, then, in principle, therefore, is one, one, a big, a big hit, right? For you and your family, and those around you. Then, then, assuming you go a little, and then have a period of uncertainty, not knowing what it really is.” (ESP)

However, increasing disease and treatment burden over time would also negatively impact how people felt and their motivation to self-manage.

“I stopped with the medication...already almost one year... Because I was annoyed to administer an injection that often.” (DE)

“...sometimes I just don't feel like doing it. I would think: Oh I can't be doing with doing it today.... I feel like it is sticking this needle into me and it is doing God knows what to my fat and my skin. Sometimes I think: I will just give it a break today.” (UK)

“I am okay some days, but I cry a lot, if I am by myself, because I think oh, I can't cope, I can't do this, you know, like, sometimes, even going to the supermarket, because my legs are so painful, that then, when I go to the supermarket, I will be in floods of tears about having to go, because I think how am I going to cope with a trolley and things.” (UK)

Sub-theme: Treatment Impact

“Injecting day in, day out doesn't allow you to forget the illness” (ESP)

Across the sample, treatment was shown to have both a positive and negative impact on people. For some, taking treatment went beyond just being something to manage the illness but was also a way to feel in control.

“Through the medicine I can [control MS]...because the medication I am currently taking, since I use this medicine...it’s so good to me now”

(DE)

“My perspective is that if you don’t do everything that you can and something goes wrong, then you are going to regret it for the rest of your life” (UK)

Using treatment as a way to exert control held true for some people even when the immediate impact was not evident (see theme Anticipated Regret on this).

Conversely, some people talked about the negative impact that following treatment regimens had on them. For some, having to follow a treatment regimen was impactful psychologically as it served as a reminder that they were unwell or added to what already seemed a burdensome disease.

“Injecting is depressing. It makes you feel like a sick person. Injecting day in, day out doesn’t allow you to forget the illness.” (ESP)

“So you had to keep a diary of when you were doing it and stuff. It was quite hard work...it was just a bit of a pain...it got to be like schoolwork in the end. I was kind of filling it in and then kind of making it up...I was filling it in and then thinking well I must have done it there then and that makes that, it wasn’t a true reflection of it...I would’ve preferred not to have to do it.” (UK)

Equally, the physical burden of treatment, in particular injection treatments, could have a negative impact on people and their desire to stay on treatment.

“It was difficult for me to inject oneself with the medication...however taking every day an oral medication.... this is really easy...” (DE)

“Yes. I can’t use the automatic thing, because I couldn’t stand the noise of the click, so I do it manually. It is not that it hurts, because I put cream on that is fine, it is just every time I come to do it, I think oh God, I really don’t want to do it again... so I am seeing the hospital in January to discuss what other things I could do.” (UK)

For some this was then compounded by perceptions of treatment efficacy.

“I always think what is the point, because if you are diabetic and you take your injection, it is to stop you getting really ill that day. Whereas I think I don’t know whether it is doing anything for me or not.” (UK)

“Because I find it hard when it is not a cure, it is not a thing that makes you feel better, it just makes you feel rubbish” (UK)

The experience of side effects was also cited as a reason for discontinuation or non-adherence with treatment.

“If the side effects are extremely, then you should stop taking the drug...but I would always look for an alternative medication...” (ESP)

However, some people did find ways to try to actively reduce their side effects so that they could persist with treatment.

“I always took it last thing at night, so the side effects would hopefully be during the night.” (UK)

“I have to inject three times a week and usually I do at night because you have some effects, as very cold, so I am in bed” (ESP)

Theme: Coping

As described above, people would put coping mechanisms in place to try to mitigate the impact of MS across a number of dimensions (e.g. psychological, treatment). This was a form of direct control (e.g. where treatment obviously reduced relapses or learning pacing techniques to reduce fatigue) but it was also evident for some people that simply feeling in control was an important psychological ‘state’ – often driving or helping to maintain coping behaviours even in the absence of an overt physical effect. When looking at the types of coping mechanisms people put in place, it was evident from across the sample that there were two ‘types’; adaptive and avoidance behaviours. Adaptive behaviours were linked to acceptance of the condition and were, on the whole, positive. Avoidance behaviours were still a way of coping, but on the whole were more ‘negative’ or short sighted, these seem particularly prevalent at diagnosis and early stages of MS, as people took time to accept and adjust to the changes, or where the physical impact was still relatively ‘mild’. However, for some there was a balance to be struck

– acceptance and actively doing what they could to manage, but with a degree of trying to minimise the impact through not focussing on it more than needed or ‘taking each day as it comes’.

Sub-theme: Adaptive

“Learning your limits...it’s about listening to your body you’re your needs” (UK)

Many individuals found that their MS and treatment regimens were easier to cope with once they had made some necessary adjustments to their day-to-day living.

“yeah you have to adjust your lifestyle. You have to do it. You can’t...because you end up basically making yourself a lot worse...not necessarily in a permanent way but certainly, now I know the warning signs and I know when to stop.” (UK)

“I think, that I’m excluded from many activities that I could have done before I got my disease. But I am looking for other activities which are feasible.” (DE)

“Well, then, in every way, right? At work, at home, in the family, friends, everything...you cut your lifestyle, right? Now you have to adapt.” (ESP)

Decisions to make conscious adaptations were often linked to acceptance of their condition and the circumstances around it, such as this participant talking about working with their psychologist to help them come to terms with using their walking stick.

“She gets me to see it [MS]...in a different way. So she got me to realise that I needed that walking stick and it makes more sense to use that and overcome the emotional side of it...so instead of letting it get me down, I kind of look at it in a more positive way as in, actually, that gets me out. Without that, I would just be in the house and I wouldn’t be able to get anywhere, so it is almost like you have to befriend that because that is, you know, what is going to, kind of, give you your lease of life, really.”
(UK)

This was also linked to more positive psychological outcomes for some.

“...right, okay, hang on, slow down a wee bit, do this, do it that way, do it this way and just kind of plan it out a wee bit. But definitely as well, I think keeping a positive attitude - that definitely, definitely helps... and speaking to people where needed.” (UK)

However, for some, acceptance and compliance appeared to be tinged with a degree of fatalism, as if the individuals had surrendered themselves to the fate that MS had in store for them or had even relinquished their own sense of control.

“I mean it’s not so much about control, it’s dealing with it basically... basically, I’ve got a five-year-old girl so it’s something I just have to get on and live with. I rest as much as I can...other than that you just have to basically put up with it, you’ve got it.” (UK)

“I do not know specifically how it serves well. I do not know; I would not know what to tell you. But they say there is this medicine and you do it.”

(ESP)

Sub-theme: Avoidance

“I am stubborn, and I don’t want to accept I have got MS” (UK)

Comparatively, there were some individuals who appeared to be more avoidant in their coping style – or who referenced stages in their disease, particularly early on, that they had tried to deal with MS by ignoring what was happening.

“It changed everything and it just took me a long time to come to terms with it, even though I had known I had had it for that long. I think I must have been in some sort of denial and part of me was hoping it was something else for all those four years that I had kept it to myself.” (UK)

For some, it was important to try and get a balance between managing the condition but not letting it ‘rule’ their lives, therefore they adopted behaviours that allowed them to avoid having to focus on their MS too much, including taking their medication.

“It never goes away, it is a worry and it affects everything, whereas when you are taking medication it pushes it more to the back of your mind. It is there but it is not taking over your mind. You are not taken over psychologically or physically.” (UK)

“I personally believe MS has 100% control over you but what you can do is live your life without knowing...well knowing you have MS but not letting it affect your day to day life as much as possible” (UK)

“I have learned with the MS to just live every day as it comes so, right now, that is firmly at the back of my mind and I just enjoy each day of my life as it is. And when that day finally arrives I will deal with it then so, right now, I don't give it a second thought.” (UK)

Avoidance of difficult and stressful situations was also a common way to try to manage their MS, though over the long term this could have a negative impact socially.

“I think you try and stay away from stress but you know I just think a lot of my friends have gone on exclusion diets and kind of trying to control it, it is controlling their lives.” (DE)

Overarching Theme: Conflict

People seemed to experience a number of different conflicts in their experience of living with and managing of MS. There were social conflicts, such as a desire to maintain independence versus the practical need to seek help from others, or the need to reduce activities versus wanting to play an active role in work / family. The use of treatment could often be a source of conflict too, with people sometimes not seeing ‘the point’ or doubting its efficacy but being too worried about what might happen if they stopped to

respond to these doubts. These conflicts could sometimes manifest into feelings of guilt, particularly where friends and family were impacted, but also trying to prevent themselves feeling guilty in the future by taking action now. As described in the theme control, there was also a direct link between conflict and control, with control coming from the resolution of conflict but also a desire for control helping to resolve conflicts, or at least still prompt action, even if the underlying conflict was still there, such as in the medicine efficacy example above.

Theme: Anticipated Regret

“If you don’t do everything that you can and something goes wrong, then you are going to regret it the rest of your life” (UK)

A driver of many self-management behaviours, including adherence to treatment, was anticipated regret. People spoke about their fears for the future in relation to their MS, particularly in terms of greater disability, and it was this that led them to look after themselves now.

“Especially because I don’t want to feel worse. Now I have a normal life, more or less. I don’t want to feel worse and end up in a wheelchair.” (ESP)

“The most important thing is to stop me from getting worse. If I was disabled, I could live a normal life but because of the progressive nature of MS and I know what happens at the later stages of MS I just think anything to stop it from getting worse” (UK)

For some people this was an internal driver, in that they felt it was their responsibility and talked about the impact in terms of the direct effect on them. Others turned to or were persuaded by people in their support network to undertake positive behaviours, and they too used thoughts about potential future outcomes to try and persuade adherence or other self-management behaviours.

“It will be in the evening, when I am going there is no point, there is no point in taking an injection, what good is it, I am not going to feel any better tomorrow. And then my husband is like but you could feel worse tomorrow, we don’t know, if you stop, it might be worse” (UK)

This anticipation seemed to provide a ‘buffer’ against negative beliefs relating to treatment. For example, people would question the efficacy of the treatment, or express concerns, but still continue with treatment as they felt the potential risk of getting worse was too high.

I do just sometimes think I wonder what would happen if I didn’t take it? But I don’t think I would like to take the risk and see what would happen.” (DE)

*“I am not sure if I would have the same course of the disease, without taking the medication...I am not sure if my medication has any effect.”
(ESP)*

Theme: Guilt

"...that's one of the things I was really keen on doing from the start is, making sure I do everything possible to make sure it's never my fault," (UK)

Guilt manifested itself in a number ways across the research population, often driving 'action' in terms of self-management behaviours but also having a detrimental effect on psychological wellbeing for many. Having to ask for, or reply on the support of others, in particular friends and family, was troublesome for some.

"My dad would take me to every appointment, but I don't think it's fair on him." (DE)

"My family, my boyfriend and such but I have faced this a rather strange way because... I have always tried not have to depend on anyone.

Perhaps not aware at some point in my life later have to rely on someone." (ESP)

As seen in the previous theme, anticipated regret, guilt (or at least, anticipation of it) drove people to undertake self-management behaviours now, even if they were doubtful of their efficacy.

"I think I would feel guilty if I did start relapsing and I hadn't gone on any medication." (UK)

Interestingly, a number of people felt guilty that their condition was not as bad as other people with MS, particularly if their symptoms were not as overt as other's.

"Obviously I understand that, you know, I have got these changes in my MRI but because I am well, in myself, sometimes I feel like a bit of a fraud." (UK)

"I feel guilty because a lot of people my age are a lot worse off." (DE)

Guilt about the impact of MS on others, in particular close family, was also evident and could be a source of conflict trying to balance their needs against those of others and also the short versus long-term implications of action / inaction.

"So at Christmas we are not doing swimming anymore. Which I felt extreme guilt about, but I know I just can't carry on like that and do those sort of things. I am starting to know what my limits are." (UK)

"Now my MS is really...I'm really struggling with it...my children are struggling a little bit with it, because why is mummy not coming out with us today" (UK)

Theme: Support and Understanding

“Talking has definitely, definitely helped – definitely” (UK)

Participants talked about the impact that the reaction and support of other people had on them, in particular with relation to how supported and / or understood they felt. Where empathy and understanding were shown this would tend to lead to more positive feelings. This could come from existing social sources or was provided through MS specific support groups or new social circles.

“...it helps it because then you don't feel, you know someone else is probably going through the same thing. And where they are mums, you know they are not these intelligent doctors that think you are just being paranoid.” (UK)

“I can suggest everyone. To attend a self-help group...I am positively impressed from a self-help group...it makes a lot of sense to attend this group because you receive immediately support...information sharing with peers is good” (DE)

Conversely, where a lack of empathy was shown, this negatively impacted on people. For a number of people their experiences at diagnosis seemed to be particularly lacking in empathy, at a time when they felt it should have been forthcoming.

“I just needed someone to talk to. I asked my MS nurse three times for a counsellor... I never heard anything so I never got to see a counsellor. I felt that you need that sort of support, especially when you are first diagnosed.” (UK)

“But, yes, at that time, I just didn’t like her approach; I just thought that is a bit hard, really. I think, you know, it is a bit, a lot to take in like that.” (DE)

Some people had experienced problems at work following diagnosis, where a lack of adequate adjustment / provision was made, leading to them experiencing conflict between their personal needs and those of their workplace.

“My work made it worse and worse for me, they were making me work upstairs and they were making it incredibly hard and in the end I just had a complete nervous breakdown, we had all the crisis team involved and got the mental health team.” (UK)

As described in the ‘guilt’ theme, many participants felt a conflict between their own individual needs, and the needs of others in their lives.

The level of support and degree of understanding exhibited by HCPs was also important. Conflicting beliefs between participants own perceptions of their condition and those of the HCPs appeared to have a negative impact.

“My GPs don’t, they are scared of it.... reluctant. They’re very hesitant about giving me any other medication because of the medication I’m on. If I had any new symptoms even if I think it’s unrelated to my MS they will be referring me back to the neurology team, because I don’t know whether it’s arse covering or they don’t know or they think that’s the best route.... they will say, yes, that’s down to your MS straightaway when sometimes it’s not. Actually it feels like you’ve been a bit brushed off...” (UK)

However, participants had more positive feelings where there was a perception of understanding between participant and HCP

“And I think I’ve been pretty lucky because both doctors and nurses are very involved and have been involved in that I’m pretty good in that it does not affect me too much, to let me know...disease as this options of treatments.” (ESP)

For some, in addition to receiving support, participants felt that providing support to others, sharing their experiences and being empathetic was important.

“I have helped me if I try to help, to newly diagnosed, because more than anything, as I understand ... and as anyone, like me or someone who has been diagnosed with this, and has no support because... knows what you need at all times, right? And then, well, it is very

important that when someone tells you that you have multiple sclerosis, it therefore someone to explain that the world does not stop for that, and, and, and what will happen because you remove some of that uncertainty, I know I have.” (ESP)

Many participants felt that other people did not understand the condition and its impact, which led to feeling of isolation from others in their lives.

“My siblings are not very understanding. They don’t understand it. They just can’t understand that, I mean my sister, because my sister is a personal trainer, she is a bit like oh, come on, just use your legs, there is nothing wrong with you, you know, that sort of approach.” (UK)

Some people had found that their support network had changed as a result of their MS. There was evidence of previous friends distancing themselves and individuals simply not being able to interact with their social circle in the way that they used to.

“It can’t be like this. I am only 34. So I think that is why, when I see friends going off and doing, you know, horse riding at the weekend or, you know, going for walks and things and I think I used to do all long walks and I can’t do that anymore.” (UK)

This was relevant with both direct and indirect support, with one individual referring to it as an invisible disease.

“Because I don’t think there is a big, sort of, understanding of MS, really. It is like cancer, everybody has heard of cancer, haven’t they, whereas something like MS, unless it is close to you or within the family, I think a lot of people don’t really know or understand much about it at all.” (UK)

There were some people who felt stigmatised by their condition, often linked to the impact that the symptoms had on their day to day activities and abilities, or with being referred to as disabled.

“...because I was almost embarrassed, like, the first time I went out with the walking stick I was with my mum, and I had seen a couple of people that I knew, and I just threw my walking stick at my mum and I was, like, you hold it, I don’t want them to see me with a stick.” (UK)

Discussion

This discussion comprises of the following sections: discussion of findings aligned to the research questions; review of methods and models applied; contribution to knowledge; conclusion and implications for practice.

Discussion of findings

The lived experience of MS and how it influences adherence

This qualitative study provided insight into not only the lived experience of MS but also the impact of various factors driven by this experience on adherence behaviours. In this way it has helped to 'extrapolate' some of the mechanisms by which experiences, perceptions of these experiences and coping behaviours and appraisals of these influence behavioural outcomes.

In this sample avoidant coping behaviours appeared to be more related to lower mood / unhappiness compared to adaptive coping, which was linked to a more positive outlook. This is in line with psychological literature relating to unhelpful and helpful coping styles (Roth and Cohen, 2005). It was evident from across the sample that there was not a single effective way of coping with MS; participants employed different techniques and strategies as a response to their individual experiences with MS and these had a range of positive and negative implications. Most participants appeared to go through a process of adaptation, adapting to both their condition and to the changes in their lives as a result of their MS. Acceptance was also important, and this too manifested itself in different ways. Acceptance where participants made adjustments in their everyday life to account for their MS had positive

implications for self-management and adherence. However, as described above, for some acceptance was linked to a degree of fatalism. In these cases, acceptance was less positive as individuals were resigned to the fact that MS ultimately is in control. This may have negative implications for participant's self-management behaviour and adherence if they perceive that they have no control over what is going to happen and therefore relinquish responsibility (Jopson and Moss-Morris, 2003; Moss-Morris *et al.*, 2002).

Equally, in this sample, avoidance was not definitively a positive or negative coping style. In some cases, avoidance was used to try not to think about the condition, this type of avoidant coping style can have detrimental implications, as avoiding and not accepting the condition can be a barrier to adherence (Moss-Morris *et al.*, 2002). This is similar to comments that some people made about how taking medicines or attending appointments serve as a reminder of the condition. Conversely, avoidance was also used as a positive self-management coping strategy. This was seen when techniques were employed to avoid experiencing symptoms (in particular, adherence) so that they could put it to the back of their mind.

Unsurprisingly, living with and managing treatment for MS had a significant impact on people in many areas of their lives including their physical, psychological and social wellbeing. There was a complex interplay between these factors that influenced the way people coped with their MS and ultimately how much control they felt they had over their condition, similar to the 'hot cross bun' model proposed in Cognitive Behavioural Therapy (Sage *et al.*, 2013). This model highlights how emotions, sensations, thoughts and

behaviours all link into and influence each other, and how this is a multidirectional relationship. The accounts of the people in this research described this in different ways. For example, how physical limitations impacted their ability to do certain 'social' behaviours, which then led to negative emotions. Or how an emotional state of despondency, would lead to unhelpful self-management behaviours and a potential worsening of the condition. So, these factors can all influence self-management behaviours, in a very individualised way. Overwhelmingly, those who had strategies to support these dimensions felt more in control of their MS and better equipped to self-manage.

Similar to ways of coping, anticipated regret was neither definitively positive or negative. For some it was empowering and motivational, for others it was a source of conflict. Positive outcomes included better adherence and self-management driven by a need to not feel that they hadn't 'done their best' to reduce the future impact of MS. For some people this held true even when they didn't feel certain about the efficacy of the treatment; the potential risk of doing nothing was greater than following a treatment plan that may or may not have an impact. This supports the necessity-concerns framework, whereby it is the appropriate balance of pros and cons of a treatment that can drive adherence behaviours, rather than the absence of negative beliefs per se (Horne and Weinman, 1999). Often this was linked to symptom experiences, with a desire to reduce the likelihood of relapses key, as well as prolonging overall wellbeing. However, anticipated regret could also be a source of conflict, as people were not confident in the value of their treatment but

continued to use it anyway. In this case people were being driven by negative perceptions as opposed to positive ones, which over time may have a detrimental impact on emotional wellbeing and treatment satisfaction. Additionally, behaviours are likely to be more susceptible to change if people are not confident in the efficacy of the treatment, as they 'pros buffer' is not there.

People felt guilty on a number of levels in relation to their MS. Some people felt guilty about the impact their MS was having on other people around them, such as restrictions on family activity or needing to get additional support. Interestingly, some people felt guilty about their MS experiences in comparison to other people with MS; feeling guilty if they perceived their symptoms and circumstances to be better than others. These feelings of guilt were a source of conflict for some people, particularly when they have to make the choice between effectively managing their MS or taking the time to do the 'other' things in their life.

The people we interviewed varied in their needs for and perceptions of the support they received. The understanding of others about MS and their experiences was very important, this included understanding of friends and family, HCPs and other people with MS. Finding people who empathised and understood was reported as a positive thing and was also linked to positive behaviours in relation to self-management. Equally, other people not understanding and not being supportive lead to negative feelings, a changing social network and isolation. In addition, people appeared to feel in conflict about their support and needs. For example, conflict with regards to the

amount of support they received and their desire for independence, or their need to look after themselves and their obligations to others (e.g. family, friends). Many people found it difficult to find a balance in these conflicts, having a detrimental psychological impact and implications for their ability and desire to appropriately self-manage their condition.

The apparent overarching relationship between conflict and control could be considered a manifestation of the process of regulation proposed by the SRM. Leventhal proposes that people seek to find balance and that this is the ultimate driver of regulation behaviours (Leventhal, Meyer and Nerenz, 1980). This has been supported in research exploring general self-management behaviours in people with MS (Jopson and Moss-Morris, 2003) and this research supports these findings in relation to specific adherence behaviours. Conflicts, such as feeling okay now compared to knowledge about previous relapses or the likelihood of future increased disability, would be mitigated or at least addressed through the application of coping mechanisms (such as medicine taking) to trying and regain a sense of control. Similarly, where ways of coping were not effective, or presented additional challenges, this could cause conflict. Such as where the burden of treatment led to people wishing they could 'just try and see' what life would be like without it, even when they couldn't follow through on this for fear of the negative consequences of stopping.

Illness and treatment perceptions in the context of adherence in line with key tenets of the self-regulatory model

Control

Control was an overarching theme from the qualitative research and is one of the 5 key variables proposed by the SRM (Moss-Morris *et al.*, 2002), operationalised through the illness perception questionnaire to include both level of personal control over illness and the extent to which illness can be controlled with treatment (Jopson and Moss-Morris, 2003; Moss-Morris *et al.*, 2002). In line with proposed SRM processes, perceived control was bi-directional in that people attempted to put in place strategies to control MS and then, appraise how well these strategies, including adherence, worked. In turn this would influence perceptions of control and whether to maintain or adapt behaviours accordingly. For example, where medicine was deemed to be effective this would drive adherence, with some people even stating that this helped them to feel in control of MS, as opposed to MS controlling them. Similarly, some people were keen to try other treatments if they perceived them to be ineffective.

When talking about their sense of personal control it was often in the context of 'taking' the control from MS itself. This could be posited to link with desiring regulation. Leventhal's model is built on the premise that we respond to a health threat because it disrupts our 'status quo' and therefore we seek to, as much as possible, return to normal (Leventhal, Phillips and Burns, 2016; O'Connor, Jardine and Millar, 2008). Therefore, it is interesting to hear people describe this 'battle' between themselves and the condition and a desire to

wrestle control away from MS. It was this facet of control that led it to link into the other overarching theme of Conflict.

Duration

Overwhelmingly, people we interviewed had accepted that the course of their illness was uncertain, but that they could expect to get worse over time and that it could not be cured. Acceptance of these features of the condition, (i.e. overarching timeframe and decline over time) was synonymous with adaptation to manage and cope with the condition, supporting the role of these perceptions to influence coping procedures as outlined in the SRM (Leventhal, Phillips and Burns, 2016; O'Connor, Jardine and Millar, 2008). Some participants referred to periods where they had found it difficult to accept what was happening, particularly early on in the disease course / diagnosis, and that at this time they would 'avoid' doing things to manage it, as this would be tantamount to accepting what was happening. The role of acceptance is also cognizant with broader self-management literature in MS (Jopson and Moss-Morris, 2002).

The theme of 'Anticipated Regret' appeared to be largely driven by perceptions of duration and worsening of disease over time. Adherence to treatment in particular was driven by 'fear of the future' and not wanting to get worse or feeling that they hadn't tried everything possible to slow progression.

Cause

Causal beliefs did not feature strongly in the discourse of these patients. Where it did appear, it was in reference to the impact of their actions or psychological states, in particular stress, on relapses and symptoms, rather

than etiology. In this way, these beliefs seemed more aligned with the identity variable of illness perceptions. As there is not a known cause of MS then this is likely a contributing factor to people not talking about the root cause of the condition and referencing instead the uncertainty surrounding the disease.

Identity

As described within the causal variable, identity (symptom experience) of MS, linked to the theme 'Impact of MS' would influence coping behaviours and the success or failure of these behaviours could also be judged by changes in symptom experience. This aligns with the SRM in terms of both perceptions influencing coping procedures but also the process of appraisal of actions.

Consequences

Physical and cognitive symptoms had a substantial impact on day to day living and the consequences of this could both motivate and impair coping processes. A desire to reduce the impact of the condition, both short and long term was often a motivator for self-management behaviours. As seen in both the illness perception variable duration and the research theme 'anticipated regret' predicted potential consequences of not taking treatment led people to adhere, even if the immediate benefits were not always apparent.

Cognitive and physical consequences were also a direct barrier in terms of impairing ability to physically administer treatment or through cognitive problems that cause people to forget or, as described earlier, may actually impede an individual's ability to adequately self-regulate due to the reliance on cognitive processes.

Emotional response

Within the theme of psychological impact, it was possible to see how emotional appraisal and response to MS could impact both 'general' ability to cope and specifically motivation to adhere to treatment. Interestingly, psychological factors, in particular stress, were also linked to individual's causal perceptions, whereby people felt that if they could control their emotions 'better' this would have a positive impact on their MS symptoms.

Treatment Necessity

Perceptions of the need and importance of treatment was a definite driver of adherence behaviours, both when the 'results' of treatment were obvious (e.g. reduction in relapses) linked to relationship between the themes of treatment impact and coping but also as evidenced within the theme anticipated regret whereby people's beliefs that the treatment was important in the long-term would promote adherence in the 'here and now'. This relationship supports the hypothesis that treatment perceptions can be mediated by illness perceptions (Leventhal, Phillips and Burns, 2016).

Treatment Concerns

Concerns about treatment, in particular side effects, had directly caused people to stop taking treatment. It was also apparent that specific concerns relating to injections (e.g. site reactions, pain) negatively impacted perceptions of treatment and desire to adhere, with some people admitting to avoiding treatment on days when it seemed too overwhelming. However, similar to perceptions of treatment necessity / control, where it was felt treatment was important (necessary) people would put coping mechanisms in

place to try to mitigate the side effects, either actively (e.g. taking at night to reduce the impact of tiredness caused by treatment) or, to some extent, avoiding thinking about it 'too much' – this was often the conflict that was seen as part of anticipated regret and potential future guilt.

Operationalisation to COM-B

To allow for comparison of findings between the scoping review and the qualitative study, where possible findings have been operationalised to COM-B to see the extent to which the findings from both parts of this research are congruent and also to determine what this qualitative study has added to our understanding of drivers of adherence behaviours in people with MS.

Firstly, theme constructs were mapped to explicit factors from the revised COM-B for adherence to DMTs in people with MS. The mapping was based on my interpretation and understanding of the themes from the qualitative research and descriptions of the COM-B categories and factors. This mapping is listed in Table 9.

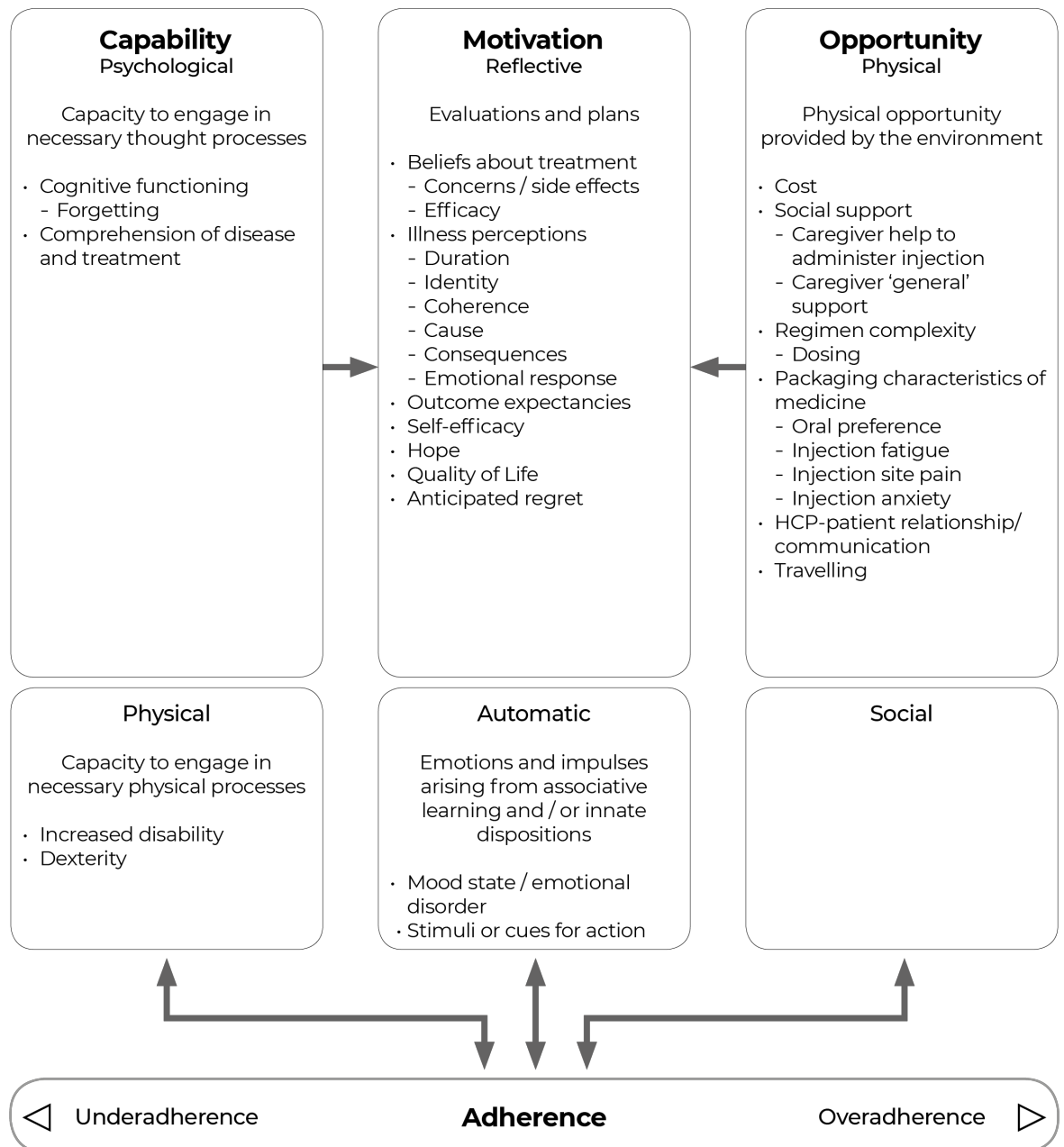
Table 9 - Mapping of COM-B for adherence in people with MS to qualitative themes

Category	Factors from review	Evident in qualitative research as impacting adherence?	Related themes
Capability (psychological)	Cognitive functioning Forgetting	Yes	Physical impact Coping Adaptive Support and understanding
Capability (physical)	Increased disability	Yes	Physical impact
Motivation (reflective)	Beliefs about treatment Concerns / side effects Efficacy	Yes	Treatment impact Coping Adaptive Conflict Anticipated regret
	Self-efficacy	Yes	Coping mechanisms
	Hope Quality of Life	No Yes	Physical impact Treatment impact Coping Adaptive
Motivation (automatic)	Mood state / emotional disorder	Yes	Psychological impact Coping Adaptive Avoiding Conflict Guilt
Opportunity (physical)	Cost	No	
	Social support Caregiver help to administer injection	Yes	Physical impact Coping Adaptive Avoidant Support and understanding Guilt
	Social support Caregiver 'general' support	Yes	Physical impact Coping Adaptive Support and understanding Guilt
	Regimen complexity Dosing	Yes	Treatment impact Coping Avoidant Adaptive Conflict Support and understanding Guilt Anticipated regret
	Packaging characteristics of medicine Oral preference Injection fatigue Injection site pain Injection anxiety	Yes	Treatment impact Coping Avoidant Adaptive Conflict Support and understanding Guilt Anticipated regret
	HCP-patient relationship/communication Physician support of treatment	Yes	Treatment impact Support and understanding
	Travelling	Yes	Physical impact Coping Adaptive
Opportunity (social)	n/a		

Secondly, additional factors from the qualitative research were then, where relevant, mapped to factors from the original COM-B for adherence that had not been evident from the scoping review (Jackson *et al.*, 2014). Finally, any additional factors from the qualitative research that mapped to categories but not original factors were added. This provided an updated COM-B for adherence to DMTs in people with MS (see Figure 8).

As stated earlier in this thesis, whilst COM-B is designed to be theory agnostic, it is a method by which to operationalise theoretical constructs and within the model published for adherence (Jackson *et al.*, 2014) there are key elements of SRM (illness perceptions, treatment beliefs, emotional response) already included, that have been discussed in this previous section.

Figure 8 - Revised COM-B for adherence to DMTs in people with MS – incorporating qualitative findings



Congruence of factors from the review and the qualitative research

Some participants felt that their impaired cognitive functioning, due to MS, did impact their ability to remember treatment and, to ensure adherence, needed to put contingencies in place to mitigate this. These could be both practical and social, such as routine development or having someone else manage the scheduling of treatments. As described earlier, forgetting as a discreet factor was omitted from the COM-B for adherence published by Jackson and colleagues (2014) as it was deemed to have too many potential confounding influences, such as motivation or lack of understanding. In addition, there is a risk of social desirability leading to this factor being 'overrepresented' as it is perceived to be more acceptable than deliberate non-adherence (DiMatteo *et al.*, 2002). However, it was a consistent factor from the review, was targeted and successfully addressed by intervention and was described in the qualitative interviews as something that could impact adherence if not mitigated through coping procedures. To this end, it seems important that this is included as a factor for consideration and that support should be offered for how to reduce likelihood of forgetting, particularly in conditions such as MS where cognitive function can be impaired.

There was also support for the impact of increased disability on adherence, in particular related to ability to inject. In addition, increased disability also increased motivation to adhere / self-manage. People referred to the experiences of previous relapses and / or potential future functional decline as their reason for wanting to persist with treatment, as demonstrated by the qualitative themes of guilt and anticipated regret. Interestingly, these themes

align with behaviour change techniques such as comparative imaginings of future outcomes, threat and (unsurprisingly) anticipated regret (Michie, Atkins and West, 2014). This alignment between change in illness threat, perceived consequences of this change (or potential change) and their influence on coping procedures supports both the model of self-regulation and gives insight into the types of techniques that may be useful to promote through intervention, drawing on 'natural' occurring regulation methods (e.g. anticipated regret).

Beliefs about treatment, specifically concerns / side effects and efficacy were also evident in the qualitative narratives and have been discussed above.

The role of self-efficacy was evident in the qualitative research, in line with review findings and the COM-B model for adherence. Self-efficacy is defined as an individual's belief that they have the capabilities to carry out a specific task or tasks to reach a desired outcome (Bandura, 1989). Self-efficacy has been shown to be predictive of a broad range of health behaviours, including adherence, across a range of chronic diseases (O'Leary, 1985). Whilst, on the whole, participants didn't explicitly talk about their level of confidence to execute behaviours, it was evident through the coping procedures people adopted when they didn't feel confident (e.g. where people struggled with medication regimens and therefore relied on social support) and also the way that people referred to times where they struggled to cope linked to not feeling able to do the necessary things to manage their MS.

Hope was a specific factor from the scoping review but does not feature in the original COM-B for adherence and did not come through in the qualitative

research. As described earlier, hope is not a specific illness perception within the SRM but may tie into beliefs about future consequences and sense of personal control over the illness and has been shown to have a close association with both motivation and positive coping, underpinned by mental representations of health. Some people did talk about maintaining a positive outlook, but this was more in relation to how this helped them cope emotionally, rather than being a driver of adherence per se. Similar but more specific constructs, such as beliefs about future consequences and belief in the ability to control the condition appeared to be more closely aligned to execution of adherence behaviours, in line with other research (Lloyd *et al.*, 2009; Maikranz *et al.*, 2007).

It is well accepted that MS has been shown to negatively impact health related quality of life (HRQoL) (Klevan *et al.*, 2014; Mitchell *et al.*, 2005). HRQoL considers the impact of health status on quality of life, with consideration of physical, mental, emotional and social implications (Bullinger, 1991). In this way, it is usually utilised as an outcome, rather than a predictive measure (Rabin and deCharro, 2001). However, when we consider how the aspects of QoL described here (e.g. physical, mental etc.) align with the impact of MS factors from the qualitative model of thematic relationships and, in turn, their impact on coping behaviours, it is possible to see how the relationship may be bi-directional. This supports the SRM in terms of disease management being an ongoing process of response, action, appraisal, adapted response; rather than a static 'cause and effect' relationship (Leventhal, Phillips and Burns,

2016) and demonstrates the potential mechanisms by which QoL predicts adherence behaviour.

Research has demonstrated the impact of mood state / disorder on adherence (DiMatteo, Lepper and Croghan, 2000). It is proposed that it can impact behaviour through mechanisms such as reduction in motivation, impacting self-efficacy and through common comorbidities / symptoms such as fatigue impacting ability to execute desired behaviours. In addition, the SRM proposes the role of emotional response in influencing coping procedures alongside cognitive appraisals (Leventhal, Phillips and Burns, 2016). The impact of emotional states and response was evident from both the scoping review and the qualitative research. Furthermore, it was one of the factors that responded to behavioural intervention. It is important that the relationship between emotional distress / affect and behavioural outcomes is recognised as this reinforces the need for support to go beyond providing just practical tools and information to 'directly' facilitate behaviour. In addition, understanding and supporting psychological factors as well, will not only be of benefit to the individual themselves on an emotional level but likely have a positive influence on their ability and motivation to execute adherence behaviours.

Cost was not something that was evident from qualitative review, though this is likely to do with the healthcare system set up in each of the countries involved – namely universal healthcare where the cost of medicine is not met by the patients.

The role of social support, both practically to help with injections / medication management and also more holistically, in terms of reducing emotional impact

and providing motivation to manage was a core theme from the research, and was cognizant with findings from the review and the original COM-B. Social support in this context has been the subject of much review and has been demonstrated as a key influencing factor on health outcomes, including adherence (Shin and Kang, 2015; Tovar et al., 2013). In addition, three of the interventions reviewed provided some form of social support, even if this wasn't an explicit aim of the research. Whilst the premise of the SRM allows for consideration of social influences on appraisals and coping, it doesn't explicitly examine them and the authors themselves recognise that there is an opportunity to explore these mechanisms further (Leventhal, Phillips and Burns, 2016). Considering how much friends and family featured in people's discourse around the MS, both in terms of support given but also how people felt about the impact their condition had on those around them, and the guilt sometimes associated with that, it would seem that, when trying to understand not only the drivers of behaviour but also the mechanisms of action, explicitly reviewing social models alongside cognitive and emotional ones may be a useful addition to the tenets of the self-regulation model.

The findings from the review highlighting the challenges people experienced in relation to treatment burden were replicated in the qualitative study. Injection treatments were perceived by many as difficult to manage and all the factors from the review (fatigue, pain, anxiety) were referenced in the discourse. In this sample, people were apparently, on the whole, fairly adherent and for those who persisted with injection-based treatments, the burden was 'accepted' in relation to beliefs about the need for the medicine and fear about

the 'what if' of non-adherence, in line with the constructs of the necessity concerns framework (Horne and Weinman, 1999). Similarly, this finding also validates the inclusion of treatment perceptions as an extension of the SRM when looking specifically at adherence behaviours. Interestingly, some participants talked about their wish to 'test' the treatment; they felt that their belief in the value of persisting in the face of the challenges would be enhanced or reinforced if they could see that, without it, things were worse. This supports a finding from a qualitative synthesis of medicine taking behaviour whereby treatment holidays were a common way that people experimented with medicine to validate its effectiveness, referred to as lay testing (Pound *et al.*, 2005). However, in this sample, people did not describe acting on this desire as anticipated regret appeared to provide a buffer against actually stopping treatment, likely influenced by the perceived seriousness of the consequences of the disease.

In the review, HCP support of medication was a factor related to adherence behaviours. The COM-B for adherence includes this but with broader definition that encompasses not just treatment congruence but the quality of the overarching relationship and communication between patient and HCP.

Research has explored the impact of the healthcare professional and patient relationship on adherence (Fuentes *et al.*, 2015; Koudriavtseva *et al.*, 2012) and found it to be an important driver of adherence behaviours. It is proposed to facilitate through a number of mechanisms, including trust, understanding, motivation and, in the case of shared decision making, helping to match clinical recommendations to the desires and the prioritised outcomes of the

patient (Fuertes *et al.*, 2015; Koudriavtseva *et al.*, 2012). The narratives of the people we spoke to demonstrated how ‘bad’ experiences with HCPs had negatively impacted them emotionally and, in some cases, led to avoidant coping behaviours or restricted acceptance and adaptation. Conversely, where people felt listened to and understood, their outlook on professional advice was more positive and the ‘additional’ social support appeared to increase confidence in their ability to control and cope with MS. This acceptance of the role of the patient in discussions and decision making has been proposed to facilitate the process of self-regulation in a positive way (Pollock and Grime, 2000). Therefore, in the final proposed COM-B for adherence to DMTs in people with MS (Figure 8), it was felt that the original description of the factor was more relevant to cover all the aspects of this driver, rather than calling out one aspect as was relevant for the review findings.

Travelling was a factor added from the review that did not feature in the original COM-B for adherence. In the context of these patients, travelling was a ‘risk’ for non-adherence as it meant that normal routines and management strategies were disrupted, likely compounded by cognitive limitations and linked to the removal of their standard stimuli for action.

Factors from the COM-B model of adherence supported by this research that did not feature in the scoping review

When comparing the insights from the qualitative study to original factors in the COM-B model that did not feature in the scoping review, there were four that were supported and therefore were added back into the final proposed COM-B model for adherence to DMTs in people with MS.

The primary addition was the re-inclusion of illness perceptions within the category of reflective motivation, across the five key domains (duration, cause, identity, consequences and emotional response) (Leventhal *et al.*, 1980) plus coherence, which features in the Revised Illness Perception Questionnaire (Moss-Morris *et al.*, 2002). These are discussed above.

The role of comprehension of disease and treatment to facilitate adherence behaviours was evident through people's descriptions of what motivated them to adhere to and persist with treatment. For example, knowledge of disease course and the function of treatment to reduce relapses, rather than cure MS or manage immediate symptoms was important as this helped to manage treatment and outcome expectancies and also informed perceptions of disease consequences. As described previously, whilst education alone is not enough to change behaviour, it is a core underpinning of behavioural change and, to this end, should be considered a core factor to review when exploring potential reasons for non-adherence (Haynes, 1996). In addition, three of the interventions included in the scoping review included educational materials and discussion topics, supporting the appropriate understanding of disease and treatment, as well as targeting other adherence factors (Zetl *et al.*, 2016; Turner *et al.*, 2014; Berger, Liang and Hudmon, 2005).

In line with the findings related to the impact of increased disability and the challenges people faced with injection treatments, it was possible to re-include dexterity from the original model within physical capability.

Similarly, people talked about the stimuli and cues for action that prompted adherence behaviours, linked to routines (e.g. timing treatment use alongside

a morning cup of tea) or reminders (self-set or from others). In addition, congruent with identity illness representations, symptoms and disease experience were also a prompt, though this seemed to be more sub-conscious than routines as an absence or reduction of symptoms ('a good day') could mean that people forgot their treatment, suggesting that their usual physical experiences were prompting action, rather than 'overt' cognitive decisions.

Additional themes or findings that could be mapped to COM-B categories

There was one additional theme from the qualitative research that aligned with the category of reflective motivation that didn't appear to be appropriately covered by the other included factors; anticipated regret. From the narratives it appeared to be not only a key driver of behaviours but also a 'buffer' against potentially unhelpful beliefs such as low treatment efficacy and negative experiences such as treatment burden. I felt that this was distinct from treatment necessity as it seemed to go beyond saying 'I need this treatment' to describe the process of making a decision now to 'protect' your future self, not only from the condition but also from feeling that you, as the person in control, hadn't done all you could, when you could.

Review of methods and models applied

Qualitative methodology

The previous limited qualitative exploration of the phenomenon of adherence in people with MS and the lack of behavioural insight this had generated suggested that taking a qualitative approach to try to enhance our understanding would contribute to knowledge in this area. However, as the work to date had garnered many potential variables, and in the spirit of trying to build on existing work, the research methods allowed for the inclusion of a theoretical 'underpinning' (namely the SRM and COM-b) to guide questionnaire development and analysis, whilst still allowing for novel data to be generated.

On reflection I still feel that this was the right approach. Qualitative methods are seen as appropriate to answer questions where 'pre-emptive reduction' risks preventing discovery of insights (Atieno, 2009), something that had been apparent from the body of work so far. To this end, I feel this study did generate new insight, not only in terms of factors that could be added to or further validated in the MS specific adherence COM-B model, but also by generating a greater understanding of some of the potential mechanisms of action of these factors, as demonstrated in the model of thematic relationships that was produced from the research, prior to an application of the findings to pre-existing models.

Underpinning the research with the same model that was used in the first part of the review (COM-B) and drawing out components of the self-regulatory

model, helped to anchor the findings to prior research and give structure to the research question as a whole. The self-regulatory model, which is a dynamic, multi-level model, particularly lends itself to qualitative exploration. Whilst the key variables of illness and treatment representations have been operationalised to self-report questionnaires (Broadbent *et al.*, 2006; Horne, Weinman and Hankins, 1999) these can only tell us part of the story of self-regulation. In an area where little qualitative research has been done, work to understand the prototypes people are referencing to influence their representations and how these in turn, manifest as coping procedures and appraisals needs a deeper level of investigation than can likely be conducted through just the use of questionnaires.

There are limitations to the approach taken. By its nature, qualitative research does not seek to assign frequencies, weightings or statistical significance to its findings (Atieno, 2009). Similarly, it can be difficult to assign generalisability to the findings in qualitative research (Braun and Clarke, 2013). In a research area where there is currently little consensus, as demonstrated by the large number of adherence factors identified in the first part of the scoping review, there is a risk that qualitative research will simply add to the 'noise' rather than help us identify areas for prioritisation, or provide insights that help the few, not the many. To this end, I do not propose that this qualitative research negates the need for systematic or meta-analytic review of this research area, as posited at the end of my scoping review. However, I think the use of a-priori assumptions and models, and the combination of analysing the data 'raw' AND operationalising to the SRM and COM-B, mitigated some of the risk

of just adding noise, as evidenced by the production of a further revised version of the COM-B, which built on existing knowledge.

A particular limitation of this study, similar to the scoping review, is the fact that the analysis was conducted by one person only. Whilst guidance for the conducting of qualitative research does not negate the conducting of research and analysis independently per se (Braun and Clarke, 2013), I do feel the lack of in-depth discussion around the themes and again, as per the first review, further input and review of the operationalisation of the findings, not only made the process more difficult but reduces the reliability of the findings. Particularly as there were specific models being explored, which will influence the interpretation of the findings. Whilst the role of the researcher is fully acknowledged in qualitative research (Bishop and Yardley, 2007), I feel that this is a potential weakness of this study and, if I were doing this again, I would seek to involve the other interviewers more formally in the analysis stage.

COM-B Model

Whilst the findings from the research supported many tenets of the SRM, I feel that reviewing the findings in line with a broader model (COM-B) prevented the research from becoming too restrictive and, in this way, it fulfilled its hypothesised function to reduce the likelihood of exploring behaviour within a single construct (e.g. motivation) and to consider the physical, cognitive and socially driven elements that may also be relevant, whilst still keeping them in the context of how they influence each other. Furthermore, as this had been used in the first part of the review it seemed

relevant to carry the process through the qualitative research. As discussed previously, the use of the model to operationalise findings carries a risk of factors being found because of a priming effect, but I believe that interpreting the data first without operationalisation (though the framework did obviously build on the underlying models of the research) helped to mitigate this in at least a small way.

The addition of a new factor and the finding that not all of the factors from the 'original' COM-B model for adherence were evident from this research, further supports my proposal in the first part of this thesis, that perhaps it is enough to have this model at a category level to aid research synthesis and considerations for intervention design (Jackson *et al.*, 2014). As described by Ogden (2016), there is a potential risk that too much systemisation of health psychology, undermines the role and skills of psychologist themselves to make interpretations and recommendations based on their experience and ability to apply a human element to research, that is, at the end of the day, about how humans 'work'.

Self-regulatory model

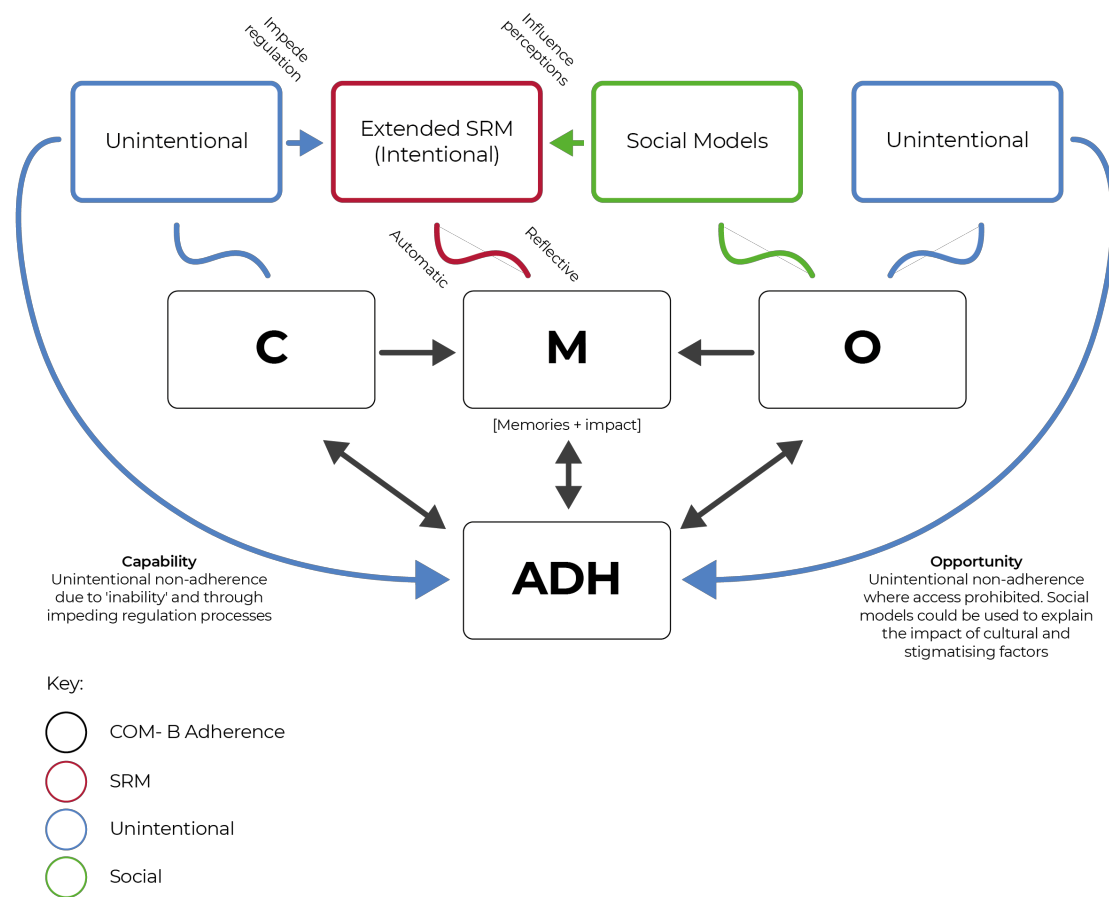
I feel that whilst this review supported many tenets of the SRM, I believe it also highlighted some areas for further consideration. The key premise of 'regulation' was supported by the findings from the qualitative review and many of the illness representations that were not evident in the scoping review were supported also. The complex and dynamic nature of adherence behaviours, and how many different factors can influence not only beliefs but the planning processes involved in executing behaviours (both explicit and

implicit) were also evident from this research and support they hypothesised way that self-regulation works (Leventhal, Phillips and Burns, 2016).

However, I feel that the SRM does not adequately account for the role of social support and considerations in the influencing of representations, coping procedures and appraisals. Both the factors review and this qualitative research demonstrated how much people with MS were 'reliant' on the support of others to help manage their condition and treatment, and also how considerations for the impact of their condition on others influenced their perceptions of the disease and motivated them to self-manage. The authors themselves acknowledge that there is more that could be done to understand the social influences (Leventhal, Phillips and Burns, 2016) and this research supports that assertion. I believe this reiterates the use of the COM-B framework to allow for extrapolation of these external factors alongside the cognitive appraisals, but I do wonder if there is an opportunity to map more formally social process either within or alongside the SRM. Figure 9 represents an example of how social models could 'fit in' to help draw out in more detail the mechanisms of action of this particular area of adherence influence, in a similar way the SRM can sit within the motivation category of COM-B. Whilst the aim is not to pre-determine the particular factors within each category, perhaps a hybrid, where recommended models / theories are assigned to the categories to aid better understanding of the mechanisms within and across each category, would be beneficial. It also incorporates findings from the first review whereby impaired cognitive function may not just

'unintentionally' impede ability to execute behaviours but also the overall process of regulation.

Figure 9 – Hypothesised mapping of models



Contribution to knowledge

This scoping review and qualitative study has contributed to our knowledge

by:

- Highlighting the current incongruence between research investigating factors influencing adherence in people with MS and the interventions designed to address these factors
- Increasing our understanding of the mechanisms of these factors in term of *how* they influence adherence through qualitative exploration
- Proposing a COM-B model for adherence that is specific for this population, built on existing research (factors review) and further validated and refined through qualitative exploration
- Identifying successful intervention techniques to address some of these factors in MS
- Proposing how COM-B may be better used to operationalise findings through the application of specific models to categories, based on the behaviour being selected, as opposed to trying to 'pre-map' discreet factors.

Conclusion

This research has highlighted the fact that, despite many years, and a relatively large volume, of research looking at drivers of adherence in people with MS, we do not yet have a core understanding of what should be prioritised in terms of trying to change that behaviour. This was borne out in the volume of discreet factors that were found, the incongruence of findings between the two scoping reviews and the additional insight that was gained from qualitative exploration.

The first scoping review identified a broad range of potential relationships, but with little consistency and stratification being identified. In addition, the methods employed and, to some extent, the premise of the research has meant that many factors identified are un-modifiable and there is little consideration for the complex relationships between factors and behaviour. The qualitative research supported this as it demonstrated that the same treatment types and symptoms could be managed and perceived differently by different people, dependent on broader factors, such as levels of perceived control, support, emotional state and priority values.

Secondly, this style of research is based on the 'strength' of findings – which is the most important factor, who is most likely to deviate from their treatment plan? As described above, this may help to identify those most 'at risk' of nonadherence (Allemann *et al.*, 2016) but does enhance our understanding of how best to support people. The qualitative findings demonstrated that managing MS is multifaceted; adherence does not occur in an isolated vacuum. To this end, trying to find the statistically significant 'silver bullet' that will solve everything is untenable. As described by Vermeire and colleagues (2001)

adherence is a flexible and somewhat elusive goal, in this instance, one size of intervention will not fit all. The relative success of skills based, individualised therapeutic interventions in enhancing both adherence and psychosocial outcomes demonstrates this. If an intervention has been able to enhance someone's overall ability to cope and feel in control, provide support and understanding and help people resolve conflicts, then as we have seen from people's own experiences, this sets them up to be able to effectively manage and respond to all the demands that living with MS, including adherence, presents.

This research has also supported the use of elements of the BCW to categorise and synthesise bodies of research, not only to aid understanding but also as a tool to build insights on the back of previous research, as demonstrated by the three variations of COM-B featuring in this work alone. It's strength in helping to 'unpick' interventions, particularly with the mapping of BCTs, was also evident as this allowed for synthesis of a range of different interventions, albeit a small sample. However, as has been said by others, this research also demonstrated that caution should probably be applied to trying to predefine lower level tenets of the BCW, such as factors within COM-B categories and the linking of techniques to intervention functions, for risk of becoming too reductive and potentially undermining the skills of the psychologist themselves. However, it's function to be able to draw out some of the relational considerations does lend itself to mappings at a more intermediate level, such as the Extended-SRM within motivation in the case of an overarching adherence model, as proposed in my mapped model.

The applicability of the SRM to this population was also evident, in particular through the qualitative narratives. People talked about how their feelings and beliefs about MS influenced their coping behaviours, both practical and emotional, and how these could be influenced by features of the disease, as well as thoughts about the past and the future. The role of regulation was also seen, in particular between the themes of conflict and control.

However, both the qualitative research and the operationalisation of factors through COM-B suggest that the SRM 'alone' is not enough to understand adherence behaviours and, if used in isolation, risks not accounting for potentially strong influencers, such as social drivers, and more discreet concepts such as guilt.

Implications for practice

This research has *somewhat* helped to better understand the phenomenon of adherence in people with MS, in particular through the revised COM-B specifically for people prescribed DMTs and the model of thematic relationships from the qualitative research. Whilst, due to the limitations already cited, these are not proposed as the final models for adherence in MS, I feel they provide a more synthesised version of the research to date from which future research can be built. In addition, the behavioural focus of this research means that these findings, including those from the second review, can hopefully better inform the design of future behavioural interventions for people with MS.

I feel that this research is also a bit of a 'call to action' in terms of trying to align research that explores the drivers of behaviour and research that tries to

modify it. Particularly as I have found this disconnect in the area of acute coronary syndrome as well (Johnston *et al.*, 2016). Continually generating data that we don't build upon, that we cannot influence is going to do little to advance our ability to positively influence adherence behaviours.

References

- Abraham, C. and Michie, S. (2008) A Taxonomy of Behavior Change Techniques Used in Interventions. *Health Psychology* [online]. 27 (3), pp.379-387.
- Adelman, R.D., Tmanova, L.L., Delgado, D., Dion, S. and Lachs, M.S. (2014) Caregiver burden: a clinical review. *Jama* [online]. 311 (10), pp.1052-1060.
- Agashivala, N., Wu, N., Abouzaid, S., Wu, Y., Kim, E., Boulanger, L. and Brandes, D.W. (2013) Compliance to fingolimod and other disease modifying treatments in multiple sclerosis patients, a retrospective cohort study. *BMC Neurology* [online]. 13 (1), pp.1.
- Allemann, S.S., Nieuwlaat, R., van den Bemt, Bart JF, Hersberger, K.E. and Arnet, I. (2016) Matching adherence interventions to patient determinants using the Theoretical Domains Framework. *Frontiers in Pharmacology* [online]. 7 .
- Arksey, H. and O'Malley, L. (2005) Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology* [online]. 8 (1), pp.19-32.
- Armstrong, D., Gosling, A., Weinman, J. and Marteau, T. (1997) The place of inter-rater reliability in qualitative research: an empirical study. *Sociology* [online]. 31 (3), pp.597-606.
- Arthur, S. and Nazroo, J. (2003) Designing fieldwork strategies and materials. *Qualitative Research Practice: A Guide for Social Science Students and Researchers* [online]. 1 pp.109-137.
- Bandura, A. (1982). Self-efficacy mechanism in human agency. *American psychologist*, 37(2), pp.122.
- Bandura, A. (1989). Human agency in social cognitive theory. *American psychologist*, 44(9), pp.1175.
- Beer, K., Müller, M., Hew-Winzeler, A.M., Bont, A., Maire, P., You, X., Foulds, P., Mårilind, J. and Curtius, D. (2011) The prevalence of injection-site reactions with disease-modifying therapies and their effect on adherence in patients with multiple sclerosis: an observational study. *BMC Neurology* [online]. 11 (1), pp.1.
- Benjamin, R.M. (2012) Medication adherence: helping patients take their medicines as directed. *Public Health Reports (Washington, D.C.: 1974)* [online]. 127 (1), pp.2-3.

Bennett, P. (2011) *Abnormal and Clinical Psychology: An Introductory Textbook* [online]. McGraw-Hill Education (UK).

Berger, B.A., Hudmon, K.S. and Liang, H. (2004) Predicting treatment discontinuation among patients with multiple sclerosis: application of the transtheoretical model of change. *Journal of the American Pharmacists Association: JAPhA* [online]. 44 (4), .

Berger, B.A., Liang, H. and Hudmon, K.S. (2005) Evaluation of softwarebased telephone counseling to enhance medication persistency among patients with multiple sclerosis. *Japha-Washington-* [online]. 45 (4), pp.466.

Bergvall, N., Petrilla, A.A., Karkare, S.U., Lahoz, R., Agashivala, N., Pradhan, A., Capkun, G., Makin, C., McGuinness, C.B. and Korn, J.R. (2014) Persistence with and adherence to fingolimod compared with other diseasemodifying therapies for the treatment of multiple sclerosis: a retrospective US claims database analysis. *Journal of Medical Economics* [online]. 17 (10), pp.696-707.

Bernstein, D., Kleinman, L., Barker, C., Revicki, D. and Green, J. (2002) Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. *Hepatology* [online]. 35 (3), pp.704-708.

Bishop, F. and Yardley, L. (2007) Qualitative Assessment . In: Ayers, S., Baum, A., McManus, C., Newman, S., Wallston, K., Weinman, J. and West, R., eds. (2007) *Cambridge Handbook of Psychology, Health and Medicine*. Cambridge University Press, pp.314-318.

Blaxter, M. and Britten, N. (1996) Lay beliefs about drugs and medicines and the implications for community pharmacy. *Pharmacy Practice Research Resource Centre, University of Manchester* [online].

Blenkinsopp, A., Bond, C., Britten, N., Feely, M., George, C., & Green, P. (1997). From compliance to concordance. *Achieving shared goals in medicine taking. A working party report. London: Royal Pharmaceutical Society of Great Britain and Merck Sharp and Dohme.*

Bloor, M. (1978) On the analysis of observational data: a discussion of the worth and uses of inductive techniques and respondent validation. *Sociology* [online]. 12 (3), pp.545-552.

Bonner, K., Mezocho, A., Roberts, T., Ford, N., & Cohn, J. (2013). Viral load monitoring as a tool to reinforce adherence: a systematic review. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 64(1), pp.74-78.

- Borras, L., Mohr, S., Brandt, P. Y., Gilliéron, C., Eytan, A., & Huguelet, P. (2007). Religious beliefs in schizophrenia: Their relevance for adherence to treatment. *Schizophrenia bulletin*, 33(5), pp.1238-1246.
- Bower, P., Harkness, E., Macdonald, W., Coventry, P., Bundy, C. and MossMorris, R. (2012) Illness representations in patients with multimorbid longterm conditions: Qualitative study. *Psychology & Health* [online]. 27 (10), pp.1211-1226.
- Brandes, K. and Mullan, B. (2014) Can the common-sense model predict adherence in chronically ill patients? A meta-analysis. *Health Psychology Review* [online]. 8 (2), pp.129-153.
- Braun, V. and Clarke, V. (2013) *Successful Qualitative Research: A Practical Guide for Beginners* [online]. Sage.
- Braun, V. and Clarke, V. (2006) Using thematic analysis in psychology. *Qualitative Research in Psychology* [online]. 3 (2), pp.77-101.
- Broadbent, E., Ellis, C.J., Thomas, J., Gamble, G. and Petrie, K.J. (2009) Further development of an illness perception intervention for myocardial infarction patients: a randomized controlled trial. *Journal of Psychosomatic Research* [online]. 67 (1), pp.17-23.
- Broadbent, E., Petrie, K.J., Main, J. and Weinman, J. (2006) The brief illness perception questionnaire. *Journal of Psychosomatic Research* [online]. 60 (6), pp.631-637.
- Bruce, J.M., Hancock, L.M., Arnett, P. and Lynch, S. (2010) Treatment adherence in multiple sclerosis: association with emotional status, personality, and cognition. *Journal of Behavioral Medicine* [online]. 33 (3), pp.219-227.
- Buhse, M. (2008) Assessment of caregiver burden in families of persons with multiple sclerosis. *Journal of Neuroscience Nursing* [online]. 40 (1), pp.25-31.
- Bull, E.R., Dombrowski, S.U., McCleary, N. and Johnston, M. (2014) Are interventions for low-income groups effective in changing healthy eating, physical activity and smoking behaviours? A systematic review and metaanalysis. *BMJ Open* [online]. 4 (11), pp.e006046.
- Bullinger, M. (1991) QUALITY-OF-LIFE-DEFINITION, CONCEPTUALIZATION AND IMPLICATIONS-A METHODOLOGISTS VIEW. *Theoretical Surgery* [online]. 6 (3), pp.143-148.
- Butler, A., Chapman, J., Forman, E. and Beck, A. (2006) The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clinical Psychology Review* [online]. 26 (1), pp.17-31.

- Campbell, N.C., Murray, E., Darbyshire, J., Emery, J., Farmer, A., Griffiths, F., Guthrie, B., Lester, H., Wilson, P. and Kinmonth, A.L. (2007) Designing and evaluating complex interventions to improve health care. *BMJ (Clinical Research Ed.)* [online]. 334 (7591), pp.455-459.
- Carter, S., Taylor, D. and Levenson, R. (2003) A question of choice: Compliance in medicine taking. [online].
- Charmaz, K. (2002) Qualitative interviewing and grounded theory analysis. In: Gubrium, J. and Holstein, J., eds. (2002) *Handbook of Interview Research: Context and Method* [online]. CA: Sage, pp.675-694.
- Clak, D.A. and Beck, A.T. (1999) *Scientific Foundations of Cognitive Theory and Therapy of Depression* [online]. John Wiley & Sons.
- Corrigan, P. (2004). How stigma interferes with mental health care. *American psychologist*, 59(7), pp.614.
- Comi, G., Filippi, M., Wolinsky, J. S., & European/Canadian Glatiramer Acetate Study Group. (2001). European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging–measured disease activity and burden in patients with relapsing multiple sclerosis. *Annals of neurology*, 49(3), pp. 290-297.
- Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., & Petticrew, M. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. *Bmj*, 337, a1655.
- Daugherty, K.K., Butler, J., Mattingly, M. and Ryan, M. (2005) Factors Leading Patients to Discontinue Multiple Sclerosis Therapies. *Journal of the American Pharmacists Association* [online]. 45 (3), pp.371-375.
- Davies, P., Walker, A.E. and Grimshaw, J.M. (2010) A systematic review of the use of theory in the design of guideline dissemination and implementation strategies and interpretation of the results of rigorous evaluations. *Implementation Science : IS* [online]. 5 (1), pp.14-14.
- De las Cuevas, C., Peñate, W., & Sanz, E. J. (2014). Risk factors for non-adherence to antidepressant treatment in patients with mood disorders. *European journal of clinical pharmacology*, 70(1), pp. 89-98.
- de Seze, J., Borgel, F. and Brudon, F. (2012) Patient perceptions of multiple sclerosis and its treatment. *Patient Preference and Adherence* [online]. 6 pp.263-273.

- Dennison, L., Moss-Morris, R., Silber, E., Galea, I., & Chalder, T. (2010). Cognitive and behavioural correlates of different domains of psychological adjustment in early-stage multiple sclerosis. *Journal of psychosomatic research*, 69(4), pp. 353-361.
- Dennison, L., Yardley, L., Devereux, A. and Moss-Morris, R. (2011) Experiences of adjusting to early stage Multiple Sclerosis. *Journal of Health Psychology* [online]. 16 (3), pp.478-488.
- Devonshire, V., Lapierre, Y., Macdonell, R., Ramo-Tello, C., Patti, F., Fontoura, P., Suchet, L., Hyde, R., Balla, I. and Frohman, E. (2011) The Global Adherence Project (GAP): A multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. *European Journal of Neurology* [online]. 18 (1), pp.69-77.
- DiMatteo, M. R., & DiNicola, D. D. (1982). Achieving patient compliance: The psychology of the medical practitioner's role.
- DiMatteo, M.R., Lepper, H.S. and Croghan, T.W. (2000) Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine* [online]. 160 (14), pp.2101-2107.
- Dimatteo, M. R., Giordani, P. J., Lepper, H. S., & Croghan, T. W. (2002). Patient adherence and medical treatment outcomes a meta-analysis. *Medical care*, pp.794-811.
- Eaddy, M.T., Cook, C.L., O'Day, K., Burch, S.P. and Cantrell, C.R. (2012) How patient cost-sharing trends affect adherence and outcomes. *Pharmacy and Therapeutics* [online]. 37 (1), pp.45-55.
- Elliott, R., Fischer, C.T. and Rennie, D.L. (1999) Evolving guidelines for publication of qualitative research studies in psychology and related fields. *British Journal of Clinical Psychology* [online]. 38 (3), pp.215-229.
- European Patients' Forum (2011) *Improving the Sustainability of Healthcare Systems through Better Adherence to Therapies: A Multi-Stakeholder Approach*. Available from: <http://www.eupatient.eu/globalassets/policy/adherence-compliance-concordance/adherence---joint-briefing-paper.pdf> [Accessed 10th December 2016].
- Faith, R., Good, R., Murgu, A. and Plotnikoff, N. (2013) *Enkephalins and Endorphins: Stress and the Immune System* [online]. Springer Science & Business Media.

Feinstein, A., Magalhaes, S., Richard, J., Audet, B. and Moore, C. (2014) The link between multiple sclerosis and depression. *Nature Reviews Neurology* [online]. 10 (9), pp.507-517.

Fernández, O., Arroyo, R., Martínez-Yélamos, S., Marco, M., Merino, J.G., Muñoz, D., Merino, E., Roque, A. and RELOAD Study Group (2016) Long-Term Adherence to IFN Beta-1a Treatment when Using RebiSmart® Device in Patients with Relapsing-Remitting Multiple Sclerosis. *PloS One* [online]. 11 (8), pp.e0160313.

Fernández, O., Agüera, J., Izquierdo, G., Millán-Pascual, J., i Torrentà, L.R., Oliva, P., Argente, J., Berdei, Y., Soler, J.M. and Carmona, O. (2012) Adherence to interferon β -1b treatment in patients with multiple sclerosis in Spain. *PloS One* [online]. 7 (5), pp.e35600.

Fraser, C., Hadjimichael, O. and Vollmer, T. (2003) Predictors of Adherence to Glatiramer Acetate Therapy in Individuals with Self-Reported Progressive Forms of Multiple Sclerosis*. *Journal of Neuroscience Nursing* [online]. 35 (3), pp.163-170.

Fraser, C., Hadjimichael, O. and Vollmer, T. (2001) Predictors of Adherence to Copaxone Therapy in Individuals with Relapsing-Remitting Multiple Sclerosis*. *Journal of Neuroscience Nursing* [online]. 33 (5), pp.231-239.

Fraser, C., Morgante, L., Hadjimichael, O. and Vollmer, T. (2004) A Prospective Study of Adherence to Glatiramer Acetate in Individuals with Multiple Sclerosis*. *Journal of Neuroscience Nursing* [online]. 36 (3), pp.120&hyphen.

Fuertes, J.N., Anand, P., Haggerty, G., Kestenbaum, M. and Rosenblum, G.C. (2015) The physician–patient working alliance and patient psychological attachment, adherence, outcome expectations, and satisfaction in a sample of rheumatology patients. *Behavioral Medicine* [online]. 41 (2), pp.60-68.

Gadkari, A.S. and McHorney, C.A. (2012) Unintentional non-adherence to chronic prescription medications: how unintentional is it really? *BMC Health Services Research* [online]. 12 (1), pp.1.

Galushko, M., Golla, H., Strupp, J., Karbach, U., Kaiser, C., Ernstmann, N., Pfaff, H., Ostgathe, C. and Voltz, R. (2014) Unmet needs of patients feeling severely affected by multiple sclerosis in Germany: A qualitative study. *Journal of Palliative Medicine* [online]. 17 (3), pp.274-281.

Girouard, N. and Soucy, N. (2011) Patient considerations in the management of multiple sclerosis: development and clinical utility of oral agents. *Patient Prefer Adherence* [online]. 5 pp.101-108.

- Glanz, B.I., Musallam, A., Rintell, D.J., Chitnis, T., Weiner, H.L. and Healy, B.C. (2014) Treatment satisfaction in multiple sclerosis. *International Journal of MS Care* [online]. 16 (2), pp.68-75.
- Hagger, M.S. and Orbell, S. (2003) A meta-analytic review of the commonsense model of illness representations. *Psychology and Health* [online]. 18 (2), pp.141-184.
- Hakim, E., Bakheit, A., Bryant, T., Roberts, M., McIntosh-Michaelis, S., Spackman, A., Martin, J. and McLellan, D. (2000) The social impact of multiple sclerosis-a study of 305 patients and their relatives. *Disability and Rehabilitation* [online]. 22 (6), pp.288-293.
- Halpern, R., Agarwal, S., Borton, L., Oneacre, K. and Lopez-Bresnahan, M.V. (2011) Adherence and persistence among multiple sclerosis patients after one immunomodulatory therapy failure: retrospective claims analysis. *Advances in Therapy* [online]. 28 (9), pp.761-775.
- Hancock, L.M., Bruce, J.M. and Lynch, S.G. (2011) Exacerbation history is associated with medication and appointment adherence in MS. *Journal of Behavioral Medicine* [online]. 34 (5), pp.330-338.
- Harrison, A. (2003) Getting the right medicines. *London: King's Fund* [online].
- Hatah, E., Lim, K. P., Ali, A. M., Shah, N. M., & Islahudin, F. (2015). The influence of cultural and religious orientations on social support and its potential impact on medication adherence. *Patient preference and adherence*, 9, pp. 589.
- Haynes, B., R., McKibbin, A., K. and Kanani, R. (1996) Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. *The Lancet* [online]. 348 (9024), pp.383-386.
- Hazell, B. and Robson, R. (2015) Pharmaceutical waste reduction in the NHS. *Report, Version* [online]. 1 .
- He, A., Spelman, T., Jokubaitis, V., Havrdova, E., Horakova, D., Trojano, M., Lugaresi, A., Izquierdo, G., Grammond, P. and Duquette, P. (2015) Comparison of switch to fingolimod or interferon beta/glatiramer acetate in active multiple sclerosis. *JAMA Neurology* [online]. 72 (4), pp.405-413.

Hoffmann, T.C., Glasziou, P.P., Boutron, I., Milne, R., Perera, R., Moher, D., Altman, D.G., Barbour, V., Macdonald, H., Johnston, M., Lamb, S.E., Dixon-Woods, M., McCulloch, P., Wyatt, J.C., Chan, A.W. and Michie, S. (2014) Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ (Clinical Research Ed.)* [online]. 348 pp.g1687.

Horne, R., Chapman, S.C., Parham, R., Freemantle, N., Forbes, A. and Cooper, V. (2013) Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. *PloS One* [online]. 8 (12), pp.e80633.

Horne, R., Weinman, J., Barber, N., Elliott, R., Morgan, M., Cribb, A. and Kellar, I. (2005) Concordance, adherence and compliance in medicine taking. *London: NCCSDO* [online]. 2005 pp.40-46.

Horne, R. and Weinman, J. (1999) Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *Journal of Psychosomatic Research* [online]. 47 (6), pp.555-567.

Horne, R., Weinman, J. and Hankins, M. (1999) The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology and Health* [online]. 14 (1), pp.1-24.

Hupperts, R., Ghazi-Visser, L., Silva, A.M., Arvanitis, M., Kuusisto, H., Marhardt, K., Vlaikidis, N. and STAR Study Group (2014) The STAR Study: a real-world, international, observational study of the safety and tolerability of, and adherence to, serum-free subcutaneous interferon β -1a in patients with relapsing multiple sclerosis. *Clinical Therapeutics* [online]. 36 (12), pp.1946-1957.

IMS Institute for Healthcare Informatics (2013) *Avoidable Costs in US Health Care*.

. Available from:

[http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/IMS%20Institute/RUOM-2013/IHII Responsible Use Medicines 2013.pdf](http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/IMS%20Institute/RUOM-2013/IHII%20Responsible%20Use%20Medicines%202013.pdf). [Accessed 10th December 2016].

Iuga, A.O. and McGuire, M.J. (2014) Adherence and health care costs. *Risk Management and Healthcare Policy* [online]. 7 pp.35-44.

Jackson, C., Eliasson, L., Barber, N. and Weinman, J. (2014) Applying COMB to medication adherence. *A Suggested Framework for Research and Interventions. the European Health Psychologist* [online]. 16 (1), pp.7-17.

Johnson, K.L., Yorkston, K.M., Klasner, E.R., Kuehn, C.M., Johnson, E. and Amtmann, D. (2004) The cost and benefits of employment: a qualitative study of experiences of persons with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation* [online]. 85 (2), pp.201-209.

Johnston, N., Weinman, J., Ashworth, L., Smethurst, P., El Khoury, J. and Moloney, C. (2016) Systematic reviews: causes of non-adherence to P2Y12 inhibitors in acute coronary syndromes and response to intervention. *Open Heart* [online]. 3 (2), pp.e000479.

Jongen, P.J., Wim, A. and Boringa, J. (2016) Persistence and adherence in multiple sclerosis patients starting glatiramer acetate treatment: assessment of relationship with care received from multiple disciplines. *Patient Preference and Adherence* [online]. 10 pp.909-917.

Jopson, N.M. and Moss-Morris, R. (2003) The role of illness severity and illness representations in adjusting to multiple sclerosis. *Journal of Psychosomatic Research* [online]. 54 (6), pp.503-511.

Katz, I. T., Ryu, A. E., Onuegbu, A. G., Psaros, C., Weiser, S. D., Bangsberg, D. R., & Tsai, A. C. (2013). Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis. *Journal of the International AIDS Society*, 16, 18640.

Kesselheim, A.S., Avorn, J. and Sarpatwari, A. (2016) The high cost of prescription drugs in the United States: origins and prospects for reform. *Jama* [online]. 316 (8), pp.858-871.

Klauer, T. and Zettl, U.K. (2008) Compliance, adherence, and the treatment of multiple sclerosis. *Journal of Neurology* [online]. 255 (6), pp.87-92.

Klevan, G., Jacobsen, C., Aarseth, J., Myhr, K., Nyland, H., Glad, S., Lode, K., Figved, N., Larsen, J. and Farbu, E. (2014) Health related quality of life in patients recently diagnosed with multiple sclerosis. *Acta Neurologica Scandinavica* [online]. 129 (1), pp.21-26.

Koudriavtseva, T., Onesti, E., Pestalozza, I.F., Sperduti, I. and Jandolo, B. (2012) The importance of physician–patient relationship for improvement of adherence to long-term therapy: data of survey in a cohort of multiple sclerosis patients with mild and moderate disability. *Neurological Sciences* [online]. 33 (3), pp.575-584.

Kripalani, S., Yao, X. and Haynes, B., R. (2007) Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Archives of Internal Medicine* [online]. 167 (6), pp.540-549.

Kucukarslan, S.N. (2012) A review of published studies of patients' illness perceptions and medication adherence: lessons learned and future directions. *Research in Social and Administrative Pharmacy* [online]. 8 (5), pp.371-382.

Kvale, S. and Brinkman, S. (2009) Interviews: Learning the craft of qualitative interviewing. [online].

Lacey, J., Cate, H. and Broadway, D. (2009) Barriers to adherence with glaucoma medications: a qualitative research study. *Eye* [online]. 23 (4), pp.924-932.

Leventhal, H., Meyer, D. and Nerenz, D. (1980) The common sense representation of illness danger. *Contributions to Medical Psychology* [online]. 2 pp.7-30.

Leventhal, H., Phillips, L. A., & Burns, E. (2016). The common-sense model of self-regulation (CSM): a dynamic framework for understanding illness self-management. *Journal of behavioral medicine*, 39(6), pp. 935-946.

Lloyd, S.M., Cantell, M., Pacaud, D., Crawford, S. and Dewey, D. (2009) Brief report: Hope, perceived maternal empathy, medical regimen adherence, and glycemic control in adolescents with type 1 diabetes. *Journal of Pediatric Psychology* [online]. 34 (9), pp.1025-1029.

Loeppke, R., Taitel, M., Haufle, V., Parry, T., Kessler, R.C. and Jinnett, K. (2009) Health and productivity as a business strategy: a multiemployer study. *Journal of Occupational and Environmental Medicine* [online]. 51 (4), pp.411-428.

Lorig, K.R., Sobel, D.S., Stewart, A.L., Brown Jr, B.W., Bandura, A., Ritter, P., Gonzalez, V.M., Laurent, D.D. and Holman, H.R. (1999) Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: a randomized trial. *Medical Care* [online]. 37 (1), pp.5-14.

Lowden, D., Lee, V. and Ritchie, J.A. (2014) Redefining self: patients' decision making about treatment for multiple sclerosis. *The Journal of Neuroscience Nursing : Journal of the American Association of Neuroscience Nurses* [online]. 46 (4), pp.E14-24.

Lugaresi, A., Florio, C., Brescia-Morra, V., Cottone, S., Bellantonio, P., Clerico, M., Centonze, D., Uccelli, A., di Iorio, M. and De Luca, G. (2012) Patient adherence to and tolerability of self-administered interferon β -1a using an electronic autoinjection device: a multicentre, open-label, phase IV study. *BMC Neurology* [online]. 12 (1), pp.1.

Lulu, S., Julian, L., Shapiro, E., Hudson, K. and Waubant, E. (2014) Treatment adherence and transitioning youth in pediatric multiple sclerosis. *Multiple Sclerosis and Related Disorders* [online]. 3 (6), pp.689-695.

Luszczynska, A., Sarkar, Y. and Knoll, N. (2007) Received social support, self-efficacy, and finding benefits in disease as predictors of physical functioning and adherence to antiretroviral therapy. *Patient Education and Counseling* [online]. 66 (1), pp.37-42.

Lysandropoulos, A. and Havrdova, E. (2015) 'Hidden' factors influencing quality of life in patients with multiple sclerosis. *European Journal of Neurology* [online]. 22 (S2), pp.28-33.

Maikranz, J.M., Steele, R.G., Dreyer, M.L., Stratman, A.C. and Bovaird, J.A. (2007) The relationship of hope and illness-related uncertainty to emotional adjustment and adherence among pediatric renal and liver transplant recipients. *Journal of Pediatric Psychology* [online]. 32 (5), pp.571-581.

Malterud, K. (2001) Qualitative research: standards, challenges, and guidelines. *The Lancet* [online]. 358 (9280), pp.483-488.

Marrie, R.A., Reingold, S., Cohen, J., Stuve, O., Trojano, M., Sorensen, P.S., Cutter, G. and Reider, N. (2015) The incidence and prevalence of psychiatric disorders in multiple sclerosis: a systematic review. *Multiple Sclerosis (Houndmills, Basingstoke, England)* [online]. 21 (3), pp.305-317.

Mays, N., Roberts, E. and Popay, J. (2001) Synthesising research evidence. *Studying the Organisation and Delivery of Health Services: Research Methods* [online]. pp.188-220.

McDonald, H.P., Garg, A.X. and Haynes, B.R. (2002) Interventions to enhance patient adherence to medication prescriptions: scientific review. *Jama* [online]. 288 (22), pp.2868-2879.

Menzin, J., Caon, C., Nichols, C., White, L.A., Friedman, M. and Pill, M.W. (2013) Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. *Journal of Managed Care Pharmacy* [online]. 19 (1 Supp A), pp.S24-S40.

Michie, S., Atkins, L. and West, R. (2014) *The Behaviour Change Wheel: A Guide to Designing Interventions*. 1st ed. London: Silverback Publishing.

Michie, S., Ashford, S., Sniehotta, F.F., Dombrowski, S.U., Bishop, A. and French, D.P. (2011a) A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy. *Psychology & Health* [online]. 26 (11), pp.1479-1498.

- Michie, S., Hyder, N., Walia, A. and West, R. (2011b) Development of a taxonomy of behaviour change techniques used in individual behavioural support for smoking cessation. *Addictive Behaviors* [online]. 36 (4), pp.315319.
- Michie, S., Richardson, M., Johnston, M., Abraham, C., Francis, J., Hardeman, W., Eccles, M.P., Cane, J. and Wood, C.E. (2013) The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Annals of Behavioral Medicine* [online]. 46 (1), pp.81-95.
- Michie, S., van Stralen, M.M. and West, R. (2011) The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implementation Science* [online]. 6 (1), pp.1.
- Michie, S., Whittington, C., Hamoudi, Z., Zarnani, F., Tober, G. and West, R. (2012) Identification of behaviour change techniques to reduce excessive alcohol consumption. *Addiction* [online]. 107 (8), pp.1431-1440.
- Miller, W. and Rose, G. (2009) Toward a theory of motivational interviewing. *American Psychologist* [online]. 64 (6), pp.527.
- Mitchell, A.J., Benito-León, J., González, J.M. and Rivera-Navarro, J. (2005) Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing. *The Lancet Neurology* [online]. 4 (9), pp.556-566.
- Mohr, D.C., Boudewyn, A.C., Likosky, W., Levine, E. and Goodkin, D.E. (2001) Injectable medication for the treatment of multiple sclerosis: the influence of self-efficacy expectations and infection anxiety on adherence and ability to self-inject. *Annals of Behavioral Medicine* [online]. 23 (2), pp.125132.
- Mohr, D. C., & Cox, D. (2001). Multiple sclerosis: empirical literature for the clinical health psychologist. *Journal of clinical psychology*, 57(4), pp. 479-499.
- Mohr, D.C., Dick, L.P., Russo, D., Pinn, J., Boudewyn, A.C., Likosky, W. and Goodkin, D.E. (1999) The psychosocial impact of multiple sclerosis: exploring the patient's perspective. *Health Psychology* [online]. 18 (4), pp.376.
- Mohr, D.C., Likosky, W., Bertagnolli, A., Goodkin, D.E., Van Der Wende, J., Dwyer, P. and Dick, L.P. (2000) Telephone-administered cognitive-behavioral therapy for the treatment of depressive symptoms in multiple sclerosis. *Journal of Consulting and Clinical Psychology* [online]. 68 (2), pp.356.

Moore, F., Vickrey, B., Fortin, K. and Lee, L. (2015) Two multiple sclerosis quality-of-life measures: comparison in a national sample. *Canadian Journal of Neurological Sciences/Journal Canadien Des Sciences Neurologiques* [online]. 42 (01), pp.55-63.

Moss-Morris, R., Weinman, J., Petrie, K., Horne, R., Cameron, L. and Buick, D. (2002) The revised illness perception questionnaire (IPQ-R). *Psychology and Health* [online]. 17 (1), pp.1-16.

MS Society UK (2016a) *Treatment and Therapies*. Available from: <https://www.mssociety.org.uk/what-is-ms/treatments-and-therapies> [Accessed 10th December 2016].

MS Society UK (2016b) *What is MS?* Available from: <https://www.mssociety.org.uk/> .

Multiple Sclerosis Australia, (2005) *Acting Positively; Strategic Implications of the Economic Costs of Multiple Sclerosis in Australia..* Canberra: Access Economics Pty Ltd.

Multiple Sclerosis Society UK (2016) *What is MS?* Available from: <https://www.mssociety.org.uk/what-is-ms> [Accessed 10 December 2016].

NICE, (2009) *Medicines Adherence: Involving Patients in Decisions about Prescribed Medicines and Supporting Adherence*. Report number: CG76.London: National Institute for Health and Care Excellence.

Nunes, V., Neilson, J., O'Flynn, N., Calvert, N., Kuntze, S., Smithson, H., Benson, J., Blair, J., Bowser, A. and Clyne, W. (2009) Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence. [online].

O'Connor, S. M., Jardine, A. G., & Millar, K. (2008). The prediction of self-care behaviors in end-stage renal disease patients using Leventhal's Self-Regulatory Model. *Journal of psychosomatic research*, 65(2), pp.191-200.

Ogden, J. (2016) Celebrating variability and a call to limit systematisation: the example of the Behaviour Change Technique Taxonomy and the Behaviour Change Wheel. *Health Psychology Review* [online]. 10 (3), pp.245-250.

O'Leary, A. (1985). Self-efficacy and health. *Behaviour research and therapy*, 23(4), pp.437-451.

Osterberg, L. and Blaschke, T. (2005) Adherence to medication. *New England Journal of Medicine* [online]. 353 (5), pp.487-497.

Patton, M. (2014) *Qualitative Research & Evaluation Methods: Integrating Theory and Practice*. 4th ed. SAGE.

Paul, L., Coulter, E.H., Miller, L., McFadyen, A., Dorfman, J. and Mattison, P.G. (2014) Web-based physiotherapy for people moderately affected with Multiple Sclerosis; quantitative and qualitative data from a randomized, controlled pilot study. *Clinical Rehabilitation* [online]. 28 (9), pp.924-935.

Pawson, R. (2002) Evidence-based policy: in search of a method. *Evaluation* [online]. 8 (2), pp.157-181.

Petrie, K.J., Cameron, L.D., Ellis, C.J., Buick, D. and Weinman, J. (2002) Changing illness perceptions after myocardial infarction: an early intervention randomized controlled trial. *Psychosomatic Medicine* [online]. 64 (4), pp.580-586.

Petrie, K.J., Perry, K., Broadbent, E. and Weinman, J. (2012) A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication. *British Journal of Health Psychology* [online]. 17 (1), pp.74-84.

Petticrew, M. and Roberts, H. (2008) *Systematic Reviews in the Social Sciences: A Practical Guide* [online]. John Wiley & Sons.

Plow, M.A., Finlayson, M. and Rezac, M. (2011) A scoping review of selfmanagement interventions for adults with multiple sclerosis. *Pm&r* [online]. 3 (3), pp.251-262.

Plow, M. and Finlayson, M. (2014) A qualitative study exploring the usability of Nintendo Wii Fit among persons with multiple sclerosis. *Occupational Therapy International* [online]. 21 (1), pp.21-32.

Pollock, K., & Grime, J. (2000). Strategies for reducing the prescribing of proton pump inhibitors (PPIs): patient self-regulation of treatment may be an under-exploited resource. *Social science & medicine*, 51(12), pp.1827-1839.

Pope, C., Ziebland, S. and Mays, N. (2000) Qualitative research in health care. Analysing qualitative data. *BMJ (Clinical Research Ed.)* [online]. 320 (7227), pp.114-116.

Pound, P., Britten, N., Morgan, M., Yardley, L., Pope, C., Daker-White, G. and Campbell, R. (2005) Resisting medicines: a synthesis of qualitative studies of medicine taking. *Social Science & Medicine* [online]. 61 (1), pp.133-155.

Rabin, R., & Charro, F. D. (2001). EQ-5D: a measure of health status from the EuroQol Group. *Annals of medicine*, 33(5), pp.337-343.

- Rio, J., Porcel, J., Tellez, N., Sanchez-Betancourt, A., Tintore, M., Arevalo, M.J., Nos, C. and Montalban, X. (2005) Factors related with treatment adherence to interferon beta and glatiramer acetate therapy in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)* [online]. 11 (3), pp.306-309.
- Ritchie, J., Lewis, J., Nicholls, C.M. and Ormston, R. (2013) *Qualitative Research Practice: A Guide for Social Science Students and Researchers* [online]. Sage.
- Ritchie, J. and Spencer, L. (2002) Qualitative data analysis for applied policy research. *The Qualitative Researcher's Companion* [online]. 573 pp.305-329.
- Roche, J., McCarry, Y. and Mellors, K. (2014) Enhanced patient support services improve patient persistence with multiple sclerosis treatment. *Patient Preference and Adherence* [online]. 8 pp.805-811.
- Rollnick, S. and Miller, W.R. (1995) What is motivational interviewing? *Behavioural and Cognitive Psychotherapy* [online]. 23 (04), pp.325-334.
- Rosenstock, I. M., Strecher, V. J., & Becker, M. H. (1988). Social learning theory and the health belief model. *Health education quarterly*, 15(2), pp.175-183.
- Rothman, A.J. (2004) " Is there nothing more practical than a good theory?": Why innovations and advances in health behavior change will arise if interventions are used to test and refine theory. *International Journal of Behavioral Nutrition and Physical Activity* [online]. 1 (1), pp.1.
- Rothman, A.J., Sheeran, P. and Wood, W. (2009) Reflective and automatic processes in the initiation and maintenance of dietary change. *Annals of Behavioral Medicine* [online]. 38 (1), pp.4-17.
- Rubin, S. E., Davis, K., & McKee, M. D. (2013). New York City physicians' views of providing long-acting reversible contraception to adolescents. *The Annals of Family Medicine*, 11(2), pp.130-136.
- Sabaté, E. (2003) *Adherence to Long-Term Therapies: Evidence for Action* [online]. World Health Organization.
- Sage, N., Sowden, M., Chorlton, E. and Edeleanu, A. (2013) *CBT for Chronic Illness and Palliative Care: A Workbook and Toolkit* [online]. John Wiley & Sons.
- Salter, A.R., Marrie, R.A., Agashivala, N., Belletti, D.A., Kim, E., Cutter, G.R., Cofield, S.S. and Tyry, T. (2014) Patient perspectives on switching diseasemodifying therapies in the NARCOMS registry. *Patient Preference and Adherence* [online]. 8 pp.971-979.

Sav, A., King, M.A., Whitty, J.A., Kendall, E., McMillan, S.S., Kelly, F., Hunter, B. and Wheeler, A.J. (2015) Burden of treatment for chronic illness: a concept analysis and review of the literature. *Health Expectations* [online]. 18 (3), pp.312-324.

Shin, N., & Kang, Y. (2015). The relationships among health locus of control and resilience, social support and health promoting behavior in patients with newly diagnosed coronary artery diseases. *Korean Journal of Adult Nursing*, 27(3), pp. 294-303.

Siegel, S.D., Turner, A.P. and Haselkorn, J.K. (2008) Adherence to diseasemodifying therapies in multiple sclerosis: Does caregiver social support matter? *Rehabilitation Psychology* [online]. 53 (1), pp.73.

Steinberg, S.C., Faris, R.J., Chang, C.F., Chan, A. and Tankersley, M.A. (2010) Impact of adherence to interferons in the treatment of multiple sclerosis. *Clinical Drug Investigation* [online]. 30 (2), pp.89-100.

Tan, H., Cai, Q., Agarwal, S., Stephenson, J.J. and Kamat, S. (2011) Impact of adherence to disease-modifying therapies on clinical and economic outcomes among patients with multiple sclerosis. *Advances in Therapy* [online]. 28 (1), pp.51-61.

Taylor-Robinson, D.C., Milton, B., Lloyd-Williams, F., O'Flaherty, M. and Capewell, S. (2008) Planning ahead in public health? A qualitative study of the time horizons used in public health decision-making. *BMC Public Health* [online]. 8 (1), pp.1.

Thannhauser, J. E., Mah, J. K., & Metz, L. M. (2009). Adherence of adolescents to multiple sclerosis disease-modifying therapy. *Pediatric neurology*, 41(2), pp.119-123.

Thorneloe, R., Bundy, C., Griffiths, C., Ashcroft, D. and Cordingley, L. (2016) Non-adherence to psoriasis medication as an outcome of limited coping resources and conflicting goals: findings from a qualitative interview study with people with psoriasis. *British Journal of Dermatology* [online].

Tolich, M. and Davidson, C. (1999) *Starting Fieldwork: An Introduction to Qualitative Research Work in New Zealand* [online]. Oxford University Press.

Tomassini, V., Paolillo, A., Russo, P., Giugni, E., Prosperini, L., Gasperini, C., ... & Pozzilli, C. (2006). Predictors of long-term clinical response to interferon beta therapy in relapsing multiple sclerosis. *Journal of neurology*, 253(3), pp.287-293.

Tovar, E., Rayens, M. K., Gokun, Y., & Clark, M. (2015). Mediators of adherence among adults with comorbid diabetes and depression: the role of self-efficacy and social support. *Journal of health psychology*, 20(11), pp. 1405-1415.

Treadaway, K., Cutter, G., Salter, A., Lynch, S., Simsarian, J., Corboy, J., Jeffery, D., Cohen, B., Mankowski, K. and Guarnaccia, J. (2009) Factors that influence adherence with disease-modifying therapy in MS. *Journal of Neurology* [online]. 256 (4), pp.568-576.

Tremlett, H., Van der Mei, I., Pittas, F., Blizzard, L., Paley, G., Dwyer, T., Taylor, B. and Ponsonby, A. (2008) Adherence to the immunomodulatory drugs for multiple sclerosis: contrasting factors affect stopping drug and missing doses. *Pharmacoepidemiology and Drug Safety* [online]. 17 (6), pp.565-576.

Tremlett, H.L. and Oger, J. (2003) Interrupted therapy: stopping and switching of the beta-interferons prescribed for MS. *Neurology* [online]. 61 (4), pp.551554.

Trisolini, M., Honeycutt, A., Wiener, J. and Lesesne, S. (2010) Global economic impact of multiple sclerosis. *Multiple Sclerosis International Federation* [online].

Turner, A.P., Roubinov, D.S., Atkins, D.C. and Haselkorn, J.K. (2016) Predicting medication adherence in multiple sclerosis using telephone-based home monitoring. *Disability and Health Journal* [online]. 9 (1), pp.83-89.

Turner, A.P., Sloan, A.P., Kivlahan, D.R. and Haselkorn, J.K. (2014) Telephone counseling and home telehealth monitoring to improve medication adherence: Results of a pilot trial among individuals with multiple sclerosis. *Rehabilitation Psychology* [online]. 59 (2), pp.136.

Turner, A.P., Williams, R.M., Sloan, A.P. and Haselkorn, J.K. (2009) Injection anxiety remains a long-term barrier to medication adherence in multiple sclerosis. *Rehabilitation Psychology* [online]. 54 (1), pp.116.

Turner, A.P., Kivlahan, D.R., Sloan, A.P. and Haselkorn, J.K. (2007) Predicting ongoing adherence to disease modifying therapies in multiple sclerosis: utility of the health beliefs model. *Multiple Sclerosis (Houndmills, Basingstoke, England)* [online]. 13 (9), pp.1146-1152.

Twook, S., Nippert, I., Scherer, P., Haas, J., Pöhlau, D. and Kugler, J. (2007) Immunomodulating drugs in multiple sclerosis: compliance, satisfaction and adverse effects evaluation in a German multiple sclerosis population. *Current Medical Research and Opinion* [online]. 23 (6), pp.1209-1215.

Vermeire, E., Hearnshaw, H., Van Royen, P. and Denekens, J. (2001) Patient adherence to treatment: three decades of research. A comprehensive review. *Journal of Clinical Pharmacy and Therapeutics* [online]. 26 (5), pp.331-342.

Wallston, K. A., Strudler Wallston, B., & DeVellis, R. (1978). Development of the multidimensional health locus of control (MHLC) scales. *Health education monographs*, 6(1), pp.160-170.

Warrender-Sparkes, M., Spelman, T., Izquierdo, G., Trojano, M., Lugaresi, A., Grand'Maison, F., Havrdova, E., Horakova, D., Boz, C., Oreja-Guevara, C., Alroughani, R., Iuliano, G., Duquette, P., Girard, M., Terzi, M., Hupperts, R., Grammond, P., Petersen, T., Fernandez-Bolanos, R., Fiol, M., Pucci, E., Lechner-Scott, J., Verheul, F., Cristiano, E., Van Pesch, V., PetkovskaBoskova, T., Moore, F., Kister, I., Bergamaschi, R., Saladino, M.L., Slee, M., Barnett, M., Amato, M.P., Shaw, C., Shuey, N., Young, C., Gray, O., Kappos, L., Butzkueven, H., Kalincik, T., Jokubaitis, V. and MSBase study group (2016) The effect of oral immunomodulatory therapy on treatment uptake and persistence in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)* [online]. 22 (4), pp.520-532.

Webb, T., Joseph, J., Yardley, L. and Michie, S. (2010) Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. *Journal of Medical Internet Research* [online]. 12 (1), pp.e4.

Weeda, E. R., Coleman, C. I., McHorney, C. A., Crivera, C., Schein, J. R., & Sobieraj, D. M. (2016). Impact of once-or twice-daily dosing frequency on adherence to chronic cardiovascular disease medications: A meta-regression analysis. *International journal of cardiology*, 216, pp.104-109.

White, C. (2001) *Cognitive Behaviour Therapy for Chronic Medical Problems: A Guide to Assessment and Treatment in Practice*. [online]. John Wiley & Sons Ltd.

Wicks, P., Rasouliyan, L., Katic, B., Nafees, B., Flood, E. and Sasané, R. (2016) The real-world patient experience of fingolimod and dimethyl fumarate for multiple sclerosis. *BMC Research Notes* [online]. 9 (1), pp.434.

Wilson, I.B. and Cleary, P.D. (1995) Linking clinical variables with healthrelated quality of life. *Jama* [online]. 273 (1), pp.59-65.

World Health Organization, (2006) *Neurological Disorders: Public Health Challenges*. WHO.

Yardley, L. (2008) Demonstrating validity in qualitative psychology. *Qualitative Psychology: A Practical Guide to Research Methods* [online]. 2 pp.235-251.

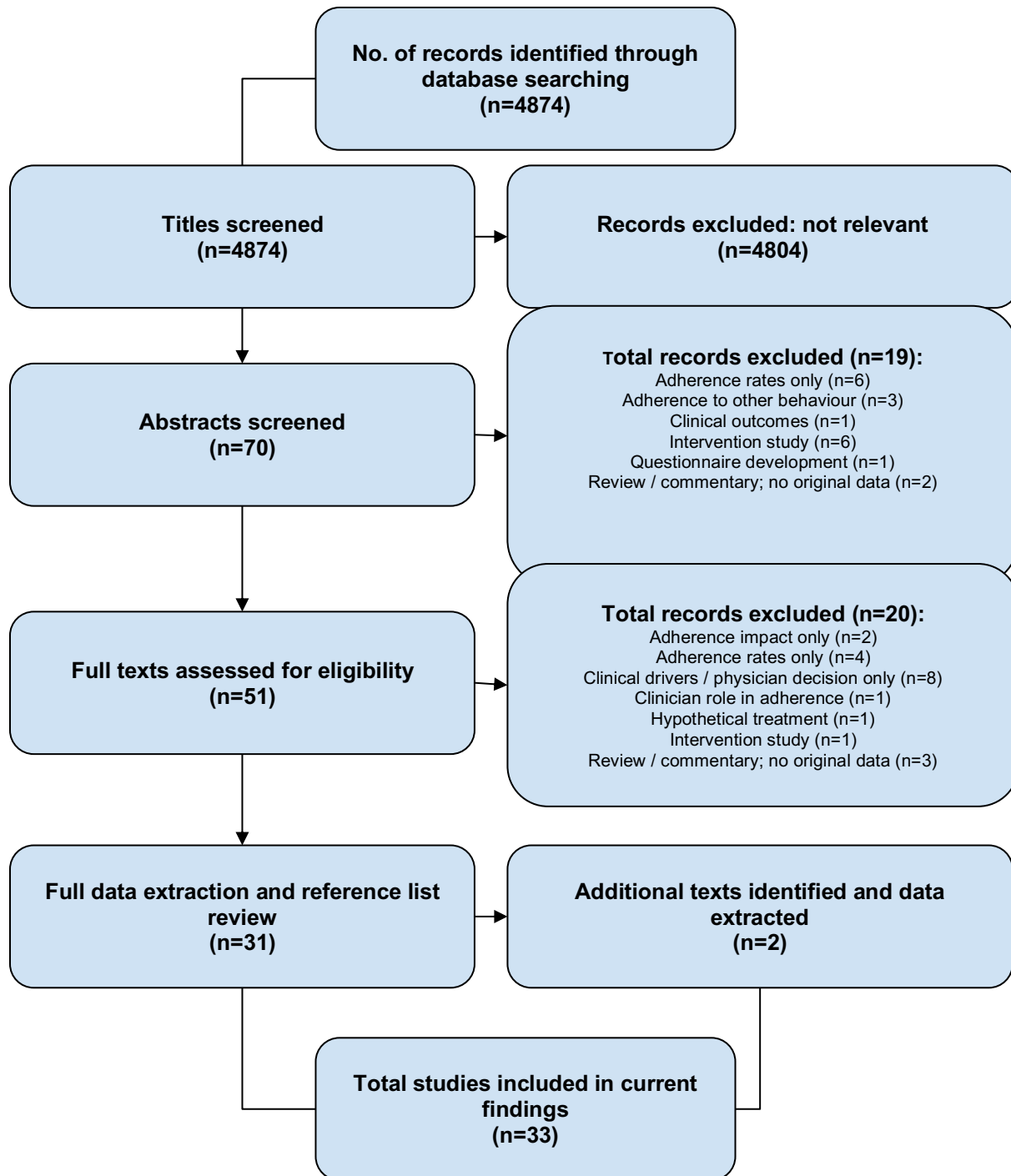
Yardley, L. (2000) Dilemmas in qualitative health research. *Psychology and Health* [online]. 15 (2), pp.215-228.

Zettl, U.K., Bauer-Steinhusen, U., Glaser, T., Czekalla, J., Hechenbichler, K., Limmroth, V. and Hecker, M. (2016) Adherence to Long-Term Interferon Beta1b Injection Therapy in Patients with Multiple Sclerosis Using an Electronic Diary. *Advances in Therapy* [online]. pp.1-14.

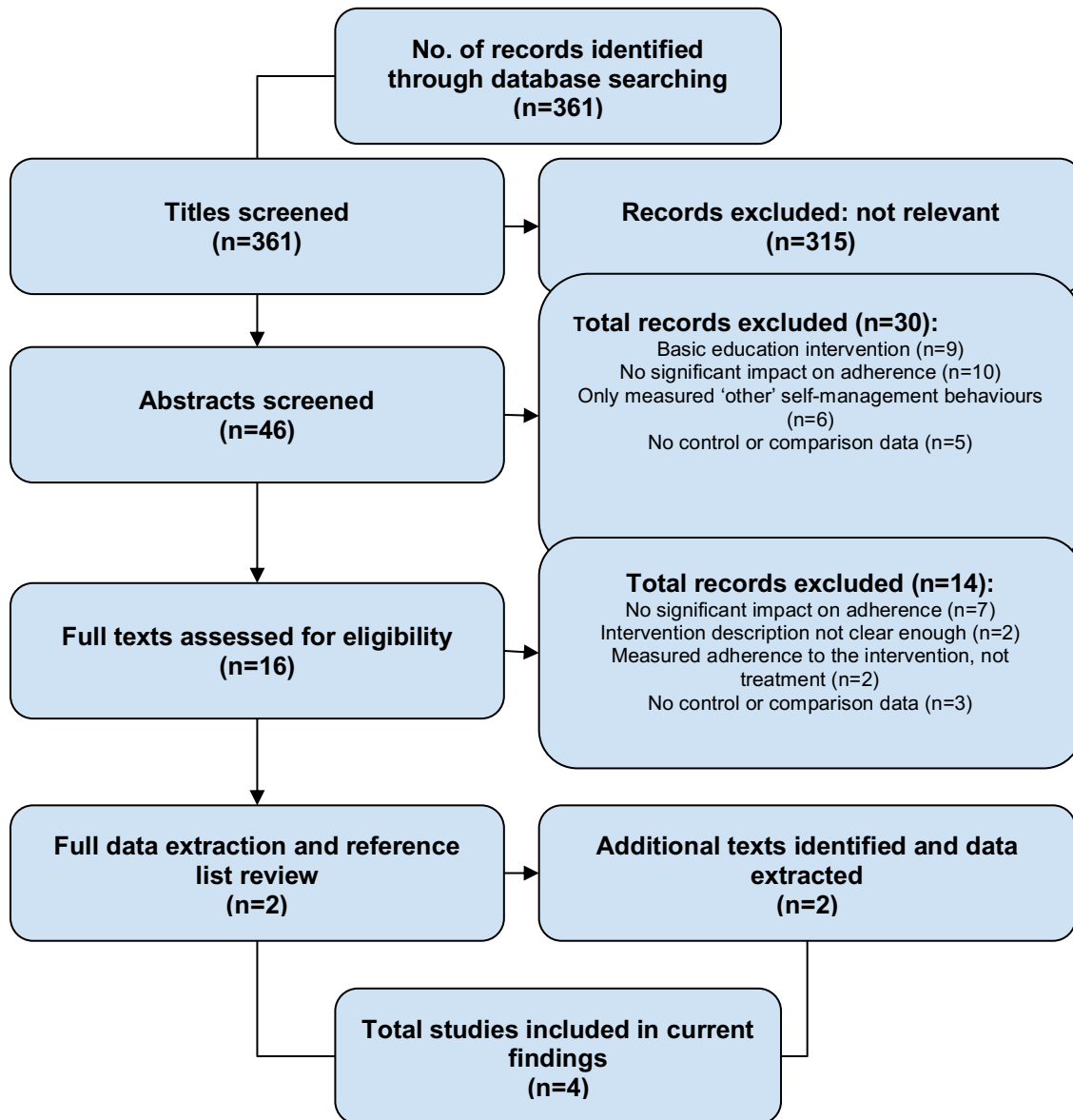
Zhornitsky, S., Greenfield, J., Koch, M.W., Patten, S.B., Harris, C., Wall, W., Alikhani, K., Burton, J., Busche, K. and Costello, F. (2015) Long-term persistence with injectable therapy in relapsing-remitting multiple sclerosis: an 18-year observational cohort study. *PloS One* [online]. 10 (4), pp.e0123824

Appendices

Appendix i: Study Selection Process Flow - Review 1 Factors impacting adherence in MS



Appendix ii: Study Selection Process Flow - Review 2 MS Adherence factors successfully modified through intervention



Appendix iii: Qualitative research supporting documents

Adherence in People with Multiple Sclerosis:

Research Materials

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Screening Questionnaire

Please select/complete as appropriate:

1. Gender – inferred by interviewer

Male		Female	
------	--	--------	--

2. What age are you?

Age (years)		If under 18, CLOSE
-------------	--	--------------------

3. Have you been diagnosed with multiple sclerosis?

Yes		Go to Q4
No		CLOSE

4. When were you diagnosed with multiple sclerosis?

DD/MM/YYYY	
------------	--

5. Do you know what type of multiple sclerosis you are diagnosed with?

Relapse-Remitting MS (RRMS)		Go to Q6
Secondary Progressive MS (SPMS)		CLOSE
Primary Progressive MS (PPMS)		CLOSE
Progressive Relapsing MS (PRMS)		CLOSE
Don't Know		CLOSE

6. Are you currently receiving treatment for multiple sclerosis?

Yes		Go to Q7
No		CLOSE

7. What treatment(s) are you currently using for your MS?

Treatment	Tick applicable
Avonex (interferon Beta 1a)	
Betaferon (interferon Beta-1b)	
Copaxone (glatiramer acetate)	
Extavia (interferon Beta- 1b)	
Gilenya (fingolimod)	
Rebif (subcutaneous interferon Beta -1a)	
Tysabri (natalizumab)	
Other (please state)	

8. Have you received any treatments for multiple sclerosis prior to your current treatment?

Yes		Go to Q9
No		Go to Q10

9. If Yes, how many?

10. What level of MS related disability do you currently have?

No symptoms	
Some symptoms, No disability	
Mild Disability	
Moderate Disability	
Severe Disability	
No Response/Not sure	

Patient Confirmation Email / Letter

This email / letter will be sent to people who have been identified by the recruitment agency as eligible for the research and have expressed an interest in taking part.

Dear [Recipient]

RE: Research exploring the experiences, perceptions and beliefs of people diagnosed with multiple sclerosis.

Following your expression of interest to take part in this research on [insert date], I am pleased to confirm that we will be calling you on [insert date] at [insert time]. You will be called by one of our interviewers and it is anticipated that the call will take approximately 45-60 minutes.

Before the interview we would like to share some further details of the research which are outlined in the Research Information Sheet that has been included with this correspondence.

In addition, we are required to get signed consent from you before conducting the interview. We have included a Consent Form with this correspondence. Please can you sign and date this once you have read the Research Information Sheet and feel confident that you are happy to proceed with the interview. This signed form can either be returned to us by post, fax or scanned into an email. The contact details to return this form are detailed below. Please be aware that as we cannot conduct the interview without this consent, it may be necessary to change the date and time of the interview if it is not received before the date detailed at the start of this **email / letter**.

We look forward to speaking with you,

Yours sincerely,

[Name]

[Title]

Include recruitment company contact details

Research Information Sheet

You have been invited to participate in this research, which is aiming to understand the experiences and perceptions of people diagnosed with multiple sclerosis and their experiences of treatment. In addition we would also like to understand your current experiences of healthcare support and identify any areas where additional support might be beneficial.

This research is being conducted by Atlantis Healthcare in association with a pharmaceutical company that creates and makes medicines and other health products.

Participating in this research involves being interviewed by a researcher over the telephone and it is anticipated that the interview will last approximately 45-50 minutes. During this interview you will be asked questions that relate to your personal health experiences, medication use and experiences, symptoms of MS, the impact of MS on you day to day and your experiences with your healthcare team.

During the research interview, it may also be necessary to collect additional safety information in relation to particular medicines / drug products, should you say something in the interview that indicates a safety risk with that product. This is known as 'Adverse Event Reporting'.

The interview will be recorded and subsequently transcribed to help us analyse the discussion. All the information collected will be kept completely confidential and will not be passed onto the healthcare professional overseeing your care for multiple sclerosis. Furthermore, comments you make during the interview will be made anonymous in our research report and you will remain completely anonymous to the pharmaceutical company who are conducting the research.

Your participation in this research will be completely voluntary, you will have the right to withdraw your participation at any time and to withhold any information you do not wish to share.

If you are interested in being involved in this research or would like to discuss it further with our team, please let us know by getting in touch by emailing or calling our central coordinator.

- **Third party recruitment agency details**

Consent Form

Title of research: Qualitative research to explore the experiences, perceptions and beliefs of people diagnosed with multiple sclerosis.

Name of researchers: Atlantis Healthcare in association with a pharmaceutical company.

Please read the statements below and tick the box to confirm that you have read and understood the information provided.

- I confirm that I have read and understand the information sheet provided for the above research and have had the opportunity to ask questions.
- I understand that my participation in this research is voluntary and that I am free to withdraw at any time, without giving any reason.
- I understand that the interviewer has an obligation to report any adverse events that are mentioned during the course of the interview.
- I give my consent to participate in this research interview.

Name of Participant

Date

Signature

Appendix iv: Approved research protocol



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Genzyme EMEA Internal Ref:
MS/EU/268/1/09/13

Adherence in People with Multiple Sclerosis

Research Protocol

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Research to explore the experiences, perceptions and beliefs of adult people with Multiple Sclerosis (MS) and their impact on adherence

Research Sponsors

Research will be sponsored by Genzyme and carried out in collaboration with Atlantis Healthcare (AH).

Rationale

This qualitative research is proposed to find out more about the experiences of people with multiple sclerosis (PwMS). This qualitative research will seek to validate findings from our literature review, from which the current programme design assumptions have been drawn (please see the 'Clinical Framework' for an outline of these factors).

This research will aim to understand the drivers and barriers in adherence to treatment and self-management behaviours in MS. Using a qualitative research technique, there will be exploration of the beliefs that are key in adherence and an investigation of current self-management processes. The outcome data will be used to inform a hypothesis of key factors that impact adherence and how these factors can inform a proposed support solution.

In the following sections the qualitative research protocol will be described, including rationale, objectives, participant sample and procedure, followed by detailed research methods.

Research objectives

Primary

- Explore the current and previous experiences of treatment for MS.
- Investigate the practical drivers and barriers in adherence to treatment for MS.
- Identify key beliefs that impact adherence to MS treatment.

Secondary

- Determine the strategies employed by PwMS to help adhere to their current or previous treatment.
- Gain insight into perceived support and informational needs of PwMS and perception of gaps in care and support.
- Explore perceptions of ability to adhere to monitoring and self-checking requirements
- Explore perceptions of proposed example screening questions.

Recruitment Strategy and Procedure

Participants

A total of 24 PwMS will be interviewed across three countries. Participants will be recruited from the UK, Germany and Spain. Eight eligible participants will be recruited from each local market for one-to-one telephone interviews. During recruitment researchers will endeavour to recruit a diverse sample of participants to reflect a range of different experiences.

Inclusion criteria:

- Diagnosed with Relapse Remitting MS (RRMS)
- Fluent speakers of first language of country of interview, or English
- Aged 18 years and over
- Currently receiving a disease modifying treatment (DMT) for MS

Desirable inclusion criteria:

- Range of socio-demographic criteria
 - Gender: aim to reflect incidence rates across the condition
 - Age: aim to include broad range of age groups (>18 years old)
 - Regional variation within each country: aim to include PwMS from a number of different district or regional hospitals, as well as specialist centres in each country

- Multiple Sclerosis factors
 - Sample to have been prescribed a range of different disease modifying treatments (DMTs)
 - Participant sample to contain a range of time since diagnosis
 - Aim to include a range of abilities:
 1. No symptoms,
 2. Some symptoms, no disability,
 3. Mild disability,
 4. Moderate disability,
 5. Severe disability

Exclusion criteria:

- Patients with severe or profound intellectual disability
- Patients who have a cognitive ability such that their level of impairment prevents them from fully understanding the research and research protocol

Recruitment

Third party market research recruitment agencies will be used to identify and recruit participants for each country. They will be contracted by Atlantis Healthcare with associated costs being passed through to Genzyme.

Procedure

PwMS meeting the inclusion criteria will be sent an invitation email or letter explaining the nature of the research, why they have been contacted and how their details were obtained. Interested participants will then be contacted to arrange an interview time that is convenient with them.

Research Methods

Qualitative interviews

The design of the current research will be a qualitative study based on semi-structured telephone interviews. Interviews will be carried out by a Health Psychology Specialist with people who are diagnosed with multiple sclerosis (PwMS). Expected duration of interviews will be 45 to 60 minutes per interview.

The interviewer will follow an interview guide stating general themes and questions to be explored, accompanied by suggested prompts and sub-questions. The interviewer will also have the flexibility to bring up new questions during the interview as a result of what the interviewee says.

Each interview will be recorded and transcribed verbatim to allow for subsequent analysis.

Rationale

A qualitative approach allows the key issues to be explored in greater depth and detail. The aim of qualitative research in this context is to gain detailed insights into PwMS's lived experience of healthcare and illness, and also the processes involved in health related behaviours (Bishop and Yardley, 2007).

One-to-one interviews have been chosen as this will allow us to get detailed insights into individual perspectives and experiences. In addition, as the topic of their illness is potentially sensitive, it is hoped that one-to-one interviews will encourage more open responses and allow for 'minority responses' which may not come out in a patient focus group (Bishop and Yardley, 2007).

Sampling strategy

This research will use purposeful sampling in order to explore a range of perspectives of the PwMS. In the context of qualitative research, purposeful sampling involves seeking out participants with particular experiences relating to the objectives of the research. This evokes more in-depth understanding of the topic as a pose to making empirical generalizations (Patton, 2002). In the current research, researchers will endeavour to recruit a diverse sample of participants with a range of different socio-economic characteristics (e.g. age, gender, religion etc.).

Data analysis plan

The interview content will initially be transcribed in preparation for data analysis. The qualitative data will then be analysed using a framework analysis approach as outlined by Ritchie and Spencer (1994). Framework analysis is used to elicit and identify commonly expressed patterns (themes) within qualitative data. This information can then be used to interpret aspects of the research topic and draw meaningful conclusions.

Ethical Considerations

Regulatory approvals

This research will not commence before it has received approval from Genzyme for the research protocol and all research materials. This includes approval of interview schedules, participant information sheets and patient screeners.

The research will be conducted in accordance with the ethical guidelines for conducting research with human participants as outlined by the European Pharmaceutical Market Research Association (EphMRA) in the European Healthcare Market Research regulations.

Informed consent and participant information

Participants will be required to give informed consent prior to taking part in the research; this will be obtained in writing prior to the interview and will be confirmed again verbally over the telephone before the interview commences. Eligible participants will be sent via post or email a formal research invitation accompanied by a consent form and an information sheet outlining the aims and procedures of the research the type of information that will be collected (e.g. related to their personal health experiences, medication use, symptoms, impact of MS on daily living and experiences with their healthcare team) and to reassure them of the confidentiality of the research. Participants will be informed that their participation is completely voluntary and they have the right to withdraw at any time without giving a reason or justification. They will also be provided with contact details should they have any questions prior to agreeing to take part in the research.

The interview call will not be scheduled until a signed consent form has been received (either by post, fax or email scanned copy). At the start of the telephone call the researcher will reiterate the important salient information as described above, including specific examples, and give the

participant the opportunity to ask questions. The researcher will ensure they are confident the information sheet has been read and understood.

The ability to give informed consent requires a sufficient level of mental and cognitive ability in order to understand what is involved in the research. Therefore, the recruitment agency will be asked to screen for any individuals who have impairments in understanding or communication that may affect their ability to give informed consent or sufficiently engage with the research process (e.g. patients with severe or profound intellectual disability or some people experiencing mental illness). However, if the researcher still has concerns over an individual's ability to give informed consent, where possible the third party organisation will be consulted for further guidance or interview terminated.

Participant confidentiality and data protection

The identity of the participants in this research will be kept strictly confidential. Their identity will not be disclosed outside of the recruitment and research team. In the case of Adverse Event reporting, participants will be specifically asked if they would like to waive their anonymity. Personal identifiable data of the participants will not be shared and data will be reported in an aggregated form to protect anonymity and confidentiality. When direct quotes are used, all identifiable information will be removed

During the data collection, audio recordings, interview transcripts, patient information sheets and consent forms will all be sent to Atlantis Healthcare offices for review and analysis. Hard copies of all research materials will be kept in a locked cupboard in a lockable room and access given to the Atlantis Healthcare research team only. Electronic data and audio recordings will be kept on a secure server in password protected files. Each participant will be allocated a unique participant ID number which will correspond to computer files, recordings and transcripts. To maintain a high level of confidentiality this coding system will also be used when sending audio files for transcription. Only the recruitment agency and the AH research team will be able to associate any data with the identity of the participant. All data will be kept for 10 years in accordance with the Data Protection Act (1998).

Potential risk to participants

The overall risk to people participating in this research study is considered to be low. The likelihood of physical risk is very low as there are no tasks or physical requirements in this research. Participants will however be asked for demographic information (i.e. age, gender) and self-reported social and emotional wellbeing with particular reference to their condition. These questions may be perceived as sensitive to some people and could evoke an emotional reaction. For this reason there may be a small likelihood of psychological risk as a result of reflecting on their condition and overall well-being. As a part of standard practice with this type of research participants will be participants will be advised at the end of each interview that, if they are experiencing any 'adverse' feelings following the interview that they may want to consider talking to someone appropriate.

Adverse events

Adverse Events will be reported in accordance with AE reporting SOPs, please see appendices i and ii.

References

Bishop, F.L. and Yardley, L. (2007). Qualitative Assessment. In: S. Ayers et al (Eds). *Cambridge Handbook of Psychology, Health and Medicine*, 2nd edition. Pp 314– 318. Cambridge University Press, Cambridge

Data Protection Act (1998). C.29. <http://www.legislation.gov.uk/ukpga/1998/29/> [Accessed 27.06.13]

Patton, M. Q. (2002). *Qualitative Research and Evaluation Methods*. London. Sage Publications Ltd.

Ritchie, J. & Spencer, L. 1994. Qualitative data analysis for applied policy research" by Jane Ritchie and Liz Spencer in A.Bryman and R. G. Burgess [eds.] *"Analyzing qualitative data"*, 1994, pp.173-194.

Appendix I: Text if a Patient Respondent Raises an Adverse Event

[Safety Information is identified and the participant is on a Genzyme/Sanofi Product]

What you [have just said] / [said earlier in the interview] is classified as safety information (NOTE: follow the definition of Safety Information as per SOP). The product manufacturer commissioning this programme (Genzyme) is required to collect this kind of information in order to continue identifying new side effects, and ways in which the risks of known side effects can be minimised. Every report they receive contains potentially useful information. I would like to spend a couple of minutes with you now to collect the necessary details of this safety information, so that the manufacturer can fulfil their obligations. Are you willing to assist with the reporting of this?

If NO: Because I have become aware of this reportable safety information, I am obliged to report this to product manufacturer. I will file this report without identifying your personal details. I may use your initials, gender or age group in case follow-up is required and I need to contact you for this. I would also recommend that you speak to your doctor so that they are aware of what you have experienced, and if necessary, follow up with you.

If YES: Thank you. The information you provide will be sent Genzyme’s Drug Safety department who, although unlikely, may wish to contact your doctor for further information. Would you like to provide the name of your doctor and allow permission to share your full name to enable them to identify yourself to your doctor?”

[Allow the patient to respond –Address any question they may have regarding the safety information report]

If the patient agrees to their personal details being included in the report, their contact details and HCP details are sent with the report.

If the patient prefers not to share their details, the report is sent de-identified and as agreed per the Safety Information Reporting SOP.

“Thank you. The information you provide will be sent to Genzyme’s Drug Safety department.

[Safety Information is identified and the participant is on a NON-Genzyme/Sanofi Product]

What you [have just said] / [said earlier in the interview] is classified as safety information and we would therefore advise that you speak to your doctor so that they are aware of what you have experienced, and if necessary, follow up with you. *[Allow the patient to respond –Address any question they may have regarding the reporting of the safety information]*

Appendix II: Adverse Event SOPs



SOP_1402-v11_(Intake_and_Reporting_of

Appendix v: EMEA Level Interview Guide

Adherence in People with Multiple Sclerosis:

Interview guide for PwMS

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Market Research Guideline Statement

This market research will be conducted in accordance with The UK Market Research Society, British Healthcare Business Intelligence Association guidelines, as well as European EphMRA guidelines.

Adverse Event Statement to be added to UK Versions:

You are about to enter a market research survey. The independent market research agency has been asked to pass on to our client details of adverse events and / or product complaints that are raised during the course of market research interviews. Your response will, of course, be treated in confidence, should you raise an adverse event and / or product complaint, the market research agency will need to report this, even if it has already been reported by you directly to the company or the regulatory authorities using the MHRA's 'Yellow Card' system. In such a situation you will be contacted to ask whether or not you are willing to waive the confidentiality given to you under the market research codes of conduct specifically in relation to that adverse event and / or product complaint. Everything else you contribute during the course of the interview will continue to remain confidential.

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Summary Rationale

This qualitative research aims to explore and understand the beliefs and adherence behaviour of adult people with multiple sclerosis (PwMS) on disease modifying treatment (DMT).

This research will explore:

- The situations, beliefs, experiences and abilities that may drive people's adherence to treatment and monitoring during MS treatment,
- Current self-management processes, perspectives of support and perceived gaps in help and support.
- Perceptions of proposed example screening questions.

Interviews will be conducted with PwMS across three countries (UK, Germany and Spain).

One-to-one interviews will be conducted by Atlantis Healthcare clinical researchers over the telephone, recorded and transcribed verbatim. The analysis will be done thematically to draw out the most important issues affecting patients' adherence and quality of life, as well as explore their current self-management strategies.

All adverse events (AEs) will be recorded and reported back to Genzyme, the client, according to their standard operating procedures and approved wording, please see appendices i and ii. All researchers involved in interviewing patients will complete training in AE reporting according to Genzyme standards prior to data collection.

Interview Schedule

The following schedule is a guide for the interviewer. The questions are not required to be read verbatim to the patient, but can be used as prompts to refer to as and when needed throughout the natural flow of the conversation. The guide is designed to help ensure that the relevant topics are covered. The precise 'course' of the interview is dependent upon the interviewee and it is the role of the interviewer to facilitate rather than lead the discussion. This flexibility allows the researcher to dig deeper into relevant issues to fully understand the interviewee's perspective to achieve the research objectives.

Introduction

(To be read verbatim)

“Thank you for agreeing to take part in this research today. My name is [state Name] and I work for a company called Atlantis Healthcare based in [state country: the UK/Germany/Spain]. We are looking to understand the experiences of people with multiple sclerosis, including what it is like to live with MS and your thoughts about different disease modifying treatment (DMT) options to help manage your condition. We are also looking to understand your experiences with healthcare professionals, of healthcare in general and to explore any additional support needs that you may have. In this study you will be asked to talk about some subjects that are sensitive and personal. For example, how you feel about having MS, the types of treatment you have had and how they have worked for you (or not), the reasons you may or not stayed with a treatment, support you may or may not have in relation to your MS and the possible emotional consequences of MS and treatment outcomes. The information from this telephone interview will be used to inform the development of a programme offering support to people with MS in living with MS and managing their treatment.

There are no right/wrong answers; we just want to explore your experiences.

Before we begin I just need to explain a few things about the study:

- This research is sponsored by a pharmaceutical company and is being carried out within the Market Research codes of conduct
 - The aim of this research is to gain your views for market research purposes only and is not intended to be promotional.
 - Anything that you are told about during this research should be treated as confidential. Any information presented during the course of this research is done so solely



to explore reactions to such information and should be assumed to represent hypotheses about what can be said about a product or disease area. It should not be used to influence decisions outside the research setting.

- The identity of respondents is confidential and none of your details will be passed on to any 3rd party.
- Outputs of this research may be used by the sponsoring pharmaceutical company in a promotional or external context at an aggregated level or using anonymised quotes.
 - This interview will be audio recorded for analysis and quality control purposes.
 - Any information you disclose will be treated in the strictest confidence and the results of the research aggregated to provide an overall picture of attitudes to the areas being covered in this survey. No answers will be attributable to you as an individual.
- You have the right to withdraw from the research at any time and to withhold information as you see fit and to refuse to be audio recorded.

Can you please confirm that you understand and accept the points that I have just read out and are happy to proceed with the interview on this basis?

Interviewer to put cross in appropriate box

- YES
- NO

[Text if a respondent says 'Yes']

This interview will take approximately 45 minutes to an hour. Are you comfortable with that?

Do you have any questions at this point?"

[Text if a respondent says 'No']

That's absolutely fine, we will not continue with the interview.

Do you have any questions before we finish this call?

[Answer / record as appropriate]

Thank you for your time.

Interview

Multiple Sclerosis

1. I'd like to begin by understanding a little more about your experiences with multiple sclerosis. Can you tell me about your condition, how and when you were first diagnosed and how it may have impacted you and your day to day life?

Aim: To understand the patient's background, how they identify with MS and the interviewee's experiences of living with their condition that may impact on their motivation to adhere.

Prompts / sub questions

Clinical Framework	Topic	Detail
	Diagnosis / Timeframe	When were you first diagnosed with multiple sclerosis? What was your experience of being told you had multiple sclerosis?
Self-efficacy / Treatment Efficacy and Necessity / Patient related outcomes / Disability and Lifestyle	Symptoms Personal Control of Condition	What symptoms affect you in your everyday life? How much control do you feel you have over your symptoms? (explore how this impacts their self-management behaviours, including adherence)
Self-efficacy	Personal Control of Condition	Do you feel you are able to control or change your MS?
	Future	What do you see happening in the future in relation to your multiple sclerosis? (explore their reasoning for what is likely to happen in the future)

Treatment experiences/beliefs

- We have talked about your experiences of living with multiple sclerosis; I'd also like to understand your experiences of disease modifying treatment (DMT) options you receive or may have previously received [check if the patient understands DMT, otherwise explain]. Can you tell me more about this?

Aim: to understand the patient's treatment experience and their beliefs about treatment/ treatment options.

Prompts / sub questions

Clinical Framework	Topic	Detail
	Previous/Current treatment	Ascertain previous and current DMTs
Motivation to adhere / Treatment Necessity and Efficacy	Experience / Timeframe	Tell me about your treatment experience with MS. How has this changed over time / with different treatments?
Treatment Efficacy / Necessity	Treatment efficacy	How effective do you think your treatment is and what does 'effective' mean to you? What has worked/what hasn't?
Practical barrier: Comprehension	Treatment understanding	Do you feel you have a good understanding of your treatments? e.g. what they are, differences and how they work?
Motivation to adhere	Treatment control	Do you feel treatment can control or change your condition? Why?
Treatment Necessity / Motivation to adhere	Medication importance	How important is your treatment? What is the most important thing about your treatment? What would be the impact on you if you didn't have any treatment for your MS?
Treatment	Side effects	Do you feel you have experienced side

concerns		effects or adverse experiences, Explore impact these have on the way the PwMS feels about a treatment and their adherence
Treatment Concerns	Concerns/Questions	Do you have any concerns or unanswered questions about your medication? (explore the impact this has on self-management and confidence)

Adherence and Persistence

3. Thinking about the treatment you have received, I want to explore how you follow or have followed your medication regimen. Many people have their own way of taking their medicines, which can be different from the instructions given by the doctors. What do you do / what is your routine?

Aim: to understand adherence and persistence to DMT

Prompts / sub questions

Clinical Framework	Topic	Detail
	Clarify	What is your current medication regimen?
Treatment Necessity / Treatment Efficacy / Motivation to Adhere	Persistence	Have you ever decided to stop using your medication? [If yes] - what made you do this / how long for? [If no] – what is it that makes / made you continue?
Treatment Necessity / Treatment Efficacy / Motivation to Adhere	Adherence	Do you follow your medication regimen as advised by HCP? Have you followed previous treatment regimens? (explore reasons for adherence or non-adherence as applicable)
	Adherence	To what extent do you follow the regimen?
Self-efficacy	Self-efficacy	Do you feel confident that you are able to follow the regimen? (explore reasons as applicable)
Treatment Necessity /	Non-adherence: reason	When you haven't followed the regimen as prescribed, what are the reasons for this?

Treatment Efficacy / Motivation to Adhere		<p>Explore reason for non-adherence (current and previous)</p> <ul style="list-style-type: none"> - <i>Change depending on how you feel? (e.g. side effects, emotional reasons, no MS symptoms)</i> - <i>Change depending on what you are doing? (e.g. holiday)</i> -
---	--	--

Self-efficacy

Clinical Framework	Topic	Detail
Self-efficacy / Cognitive Decline & Forgetting	Self-management strategies	Do you have any strategies to help you remember? (i.e. planning, reminders)
Self-efficacy / Cognitive Decline & Forgetting	Ease of self-management	Do you find it relatively easy to rather difficult to self-manage your treatment regimen? (explore reasons)
Self-efficacy / Cognitive Decline & Forgetting	Support	Do you have help with your treatment for MS? <ul style="list-style-type: none"> - From friends and family - Other support?

Self-management

Clinical Framework	Topic	Detail
Practical Barriers: Cognitive Functioning Motivation: Self-management	Self-management strategies	Would you develop any strategies to help you attend to your monitoring? (i.e. planning, reminders)
Practical Barriers: Cognitive Functioning	Ease of self-management	Would you find it relatively easy or rather difficult to self-manage compared to your current regimen?

Motivation: Self-management		
Practical Barriers: Cognitive Functioning Motivation: Self-management	Independent management / Support	Do you think you would want help with your monitoring regimen or would you manage it yourself? If you were going to have help who would you ask? <ul style="list-style-type: none"> • Friends and family? • Healthcare team? • Other?

HCP interaction

4. I'd now like to talk to you about your experiences with healthcare professionals who are involved in the treatment and management of your multiple sclerosis. Can you tell me a bit about your interactions with your doctors and nurses?

Aim: To explore the possible impact of HCP interactions and support on adherence

Prompts / sub questions

Clinical Framework	Topic	Detail
	Who is the HCP? (Background)	Without giving their personal names, which HCPs do you see in relation to your multiple sclerosis? (e.g. GP, specialist, nurse, pharmacist, other)?
Treatment Necessity / Treatment Concerns	HCP understanding	Do you feel confident that your HCP understands your experiences with your Multiple Sclerosis and your treatment?
Treatment Necessity / Treatment Concerns	Confidence in HCP	Would you feel comfortable talking to your HCP about problems or concerns you had relating to your treatment?
Self-efficacy	Monitoring assistance	Does your HCP tell or support you with how to follow the medication regimen? Would you feel confident / able to talk to your HCP about changes you had made to your treatment regime?

Support

5. We are trying to understand what type of support has been helpful for people with multiple sclerosis. Have you ever accessed a patient support programme to help with your MS?

Aim: To explore current access to patients support and investigate what has been helpful, what has not and why?

Prompts / sub questions

Topic	Detail
Patient support	Have you ever accessed a patient support programme to help with your MS or managing your treatment for MS? Yes: What treatment was it for? What did it involve? Did you / do you find it helpful?
Current support	Do you currently access a support program or group? (e.g. web forum, advocacy group)
Use/Best	What kind of support have you found most useful/best?
Not useful/Helpful	What have you not found useful or helpful?
Gaps	Currently any gaps in the support you receive or have previously received?
Would you use additional support?	Is additional support something you would use/find appealing? - Yes: Why? - No: Why?

Thank you and Conclude

Thank you very much for talking with me today. The information you've given us will be very valuable.

Thinking back to what we have discussed, is there anything else that you would like to add?



Just before we go I wanted to say that we understand it can be quite tiring to talk about these types of things in depth, so don't be surprised if you feel a little tired, or you find yourself thinking about some of the things that we have talked about. If you do feel as if you would like to talk about anything that we have discussed more, it can be a good idea to talk to someone with some expertise in this area – perhaps your GP or a member of the team at your hospital / clinic

Once again, thank you very much for taking the time to speak with us.

Appendix I Text if a Patient Respondent Raises an Adverse Event

[Safety Information is identified and the participant is on a Genzyme/Sanofi Product]

What you [have just said] / [said earlier in the interview] is classified as safety information (NOTE: follow the definition of Safety Information as per SOP). The product manufacturer commissioning this programme (Genzyme) is required to collect this kind of information in order to continue identifying new side effects, and ways in which the risks of known side effects can be minimised. Every report they receive contains potentially useful information. I would like to spend a couple of minutes with you now to collect the necessary details of this safety information, so that the manufacturer can fulfil their obligations. Are you willing to assist with the reporting of this?

If NO: Because I have become aware of this reportable safety information, I am obliged to report this to product manufacturer. I will file this report without identifying your personal details. I may use your initials, gender or age group in case follow-up is required and I need to contact you for this. I would also recommend that you speak to your doctor so that they are aware of what you have experienced, and if necessary, follow up with you.

If YES: Thank you. The information you provide will be sent Genzyme's Drug Safety department who, although unlikely, may wish to contact your doctor for further information. Would you like to provide the name of your doctor and allow permission to share your full name to enable them to identify yourself to your doctor?"

[Allow the patient to respond –Address any question they may have regarding the safety information report]

If the patient agrees to their personal details being included in the report, their contact details and HCP details are sent with the report.

If the patient prefers not to share their details, the report is sent de-identified and as agreed per the Safety Information Reporting SOP.

"Thank you. The information you provide will be sent to Genzyme's Drug Safety department.

[Safety Information is identified and the participant is on a NON-Genzyme/Sanofi Product]

What you [have just said] / [said earlier in the interview] is classified as safety information and we would therefore advise that you speak to your doctor so that they are aware of what you have experienced, and if necessary, follow up with you. *[Allow the patient to respond –Address any question they may have regarding the reporting of the safety information]*

Appendix II AE SOP



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Appendix vi: UK Interview Guide

Adherence in People with Multiple Sclerosis:

Interview guide for PwMS

Understand
Connect
Change



Market Research Guideline Statement

This market research will be conducted in accordance with The UK Market Research Society, British Healthcare Business Intelligence Association guidelines, as well as European EphMRA guidelines.

Adverse Event Statement to be added to UK Versions:

You are about to enter a market research survey. The independent market research agency has been asked to pass on to our client details of adverse events and / or product complaints that are raised during the course of market research interviews. Your response will, of course, be treated in confidence, should you raise an adverse event and / or product complaint, the market research agency will need to report this, even if it has already been reported by you directly to the company or the regulatory authorities using the MHRA's 'Yellow Card' system. In such a situation you will be contacted to ask whether or not you are willing to waive the confidentiality given to you under the market research codes of conduct specifically in relation to that adverse event and / or product complaint. Everything else you contribute during the course of the interview will continue to remain confidential.

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Summary Rationale

This qualitative research aims to explore and understand the beliefs and adherence behaviour of adult people with multiple sclerosis (PwMS) on disease modifying treatment (DMT).

This research will explore:

- The situations, beliefs, experiences and abilities that may drive people's adherence to treatment and monitoring during MS treatment,
- Current self-management processes, perspectives of support and perceived gaps in help and support.
- Perceptions of proposed example screening questions.

Interviews will be conducted with PwMS across three countries (UK, Germany and Spain). One-to-one interviews will be conducted by Atlantis Healthcare clinical researchers over the telephone, recorded and transcribed verbatim. The analysis will be done thematically to draw out the most important issues affecting patients' adherence and quality of life, as well as explore their current self-management strategies.

All adverse events (AEs) will be recorded and reported back to Genzyme, the client, according to their standard operating procedures and approved wording, please see appendices i and ii. All researchers involved in interviewing patients will complete training in AE reporting according to Genzyme standards prior to data collection.

Interview Schedule

The following schedule is a guide for the interviewer. The questions are not required to be read verbatim to the patient, but can be used as prompts to refer to as and when needed throughout the natural flow of the conversation. The guide is designed to help ensure that the relevant topics are covered. The precise 'course' of the interview is dependent upon the interviewee and it is the role of the interviewer to facilitate rather than lead the discussion. This flexibility allows the researcher to dig deeper into relevant issues to fully understand the interviewee's perspective to achieve the research objectives.

Introduction

(To be read verbatim)

“Thank you for agreeing to take part in this research today. My name is [state Name] and I work for a company called Atlantis Healthcare based in [state country: the UK/Germany/Spain]. We are looking to understand the experiences of people with multiple sclerosis, including what it is like to live with MS and your thoughts about different disease modifying treatment (DMT) options to help manage your condition. We are also looking to understand your experiences with healthcare professionals, of healthcare in general and to explore any additional support needs that you may have. In this study you will be asked to talk about some subjects that are sensitive and personal. For example, how you feel about having MS, the types of treatment you have had and how they have worked for you (or not), the reasons you may or not stayed with a treatment, support you may or may not have in relation to your MS and the possible emotional consequences of MS and treatment outcomes. The information from this telephone interview will be used to inform the development of a programme offering support to people with MS in living with MS and managing their treatment.

There are no right/wrong answers; we just want to explore your experiences.

Before we begin I just need to explain a few things about the study:

- This research is sponsored by a pharmaceutical company and is being carried out within the Market Research codes of conduct
- The aim of this research is to gain your views for market research purposes only and is not intended to be promotional.
- Anything that you are told about during this research should be treated as confidential. Any information presented during the course of this research is done so solely to explore reactions to such information and should be assumed to represent hypotheses about what can be said about a product or disease area. It should not be used to influence decisions outside the research setting.



- The identity of respondents is confidential and none of your details will be passed on to any 3rd party.
- Outputs of this research may be used by the sponsoring pharmaceutical company in a promotional or external context at an aggregated level or using anonymised quotes.
 - This interview will be audio recorded for analysis and quality control purposes.
 - Any information you disclose will be treated in the strictest confidence and the results of the research aggregated to provide an overall picture of attitudes to the areas being covered in this survey. No answers will be attributable to you as an individual.
 - You have the right to withdraw from the research at any time and to withhold information as you see fit and to refuse to be audio recorded.

Can you please confirm that you understand and accept the points that I have just read out and are happy to proceed with the interview on this basis?

Interviewer to put cross in appropriate box

- YES
- NO

[Text if a respondent says 'Yes']

This interview will take approximately 45 minutes to an hour. Are you comfortable with that?

Do you have any questions at this point?"

[Text if a respondent says 'No']

That's absolutely fine, we will not continue with the interview.

Do you have any questions before we finish this call?

[Answer / record as appropriate]

Thank you for your time.

Interview

Multiple Sclerosis

1. I'd like to begin by understanding a little more about your experiences with multiple sclerosis. Can you tell me about your condition, how and when you were first diagnosed and how it may have impacted you and your day to day life?

Aim: To understand the patient's background, how they identify with MS and the interviewee's experiences of living with their condition that may impact on their motivation to adhere.

Prompts / sub questions

Clinical Framework	Topic	Detail
	Diagnosis / Timeframe	When were you first diagnosed with multiple sclerosis? What was your experience of being told you had multiple sclerosis?
Self-efficacy / Treatment Efficacy and Necessity / Patient related outcomes / Disability and Lifestyle	Symptoms Personal Control of Condition	What symptoms affect you in your everyday life? How much control do you feel you have over your symptoms? (explore how this impacts their self-management behaviours, including adherence)
Self-efficacy	Personal Control of Condition	Do you feel you are able to control or change your MS?
	Future	What do you see happening in the future in relation to your multiple sclerosis? (explore their reasoning for what is likely to happen in the future)

Treatment experiences/beliefs

2. We have talked about your experiences of living with multiple sclerosis; I'd also like to understand your experiences of disease modifying treatment (DMT) options you receive or may have previously received [check if the patient understands DMT, otherwise explain]. Can you tell me more about this?

Aim: to understand the patient's treatment experience and their beliefs about treatment/ treatment options.

Prompts / sub questions

Clinical Framework	Topic	Detail
	Previous/Current treatment	Ascertain previous and current DMTs
Motivation to adhere / Treatment Necessity and Efficacy	Experience / Timeframe	Tell me about your treatment experience with MS. How has this changed over time / with different treatments?
Treatment Efficacy / Necessity	Treatment efficacy	How effective do you think your treatment is and what does 'effective' mean to you? What has worked/what hasn't?
Practical barrier: Comprehension	Treatment understanding	Do you feel you have a good understanding of your treatments? e.g. what they are, differences and how they work?
Motivation to adhere	Treatment control	Do you feel treatment can control or change your condition? Why?
Treatment Necessity / Motivation to adhere	Medication importance	How important is your treatment? What is the most important thing about your treatment? What would be the impact on you if you didn't have any treatment for your MS?
Treatment concerns	Side effects	Do you feel you have experienced side effects or adverse experiences, Explore impact these have on the way the PwMS feels about a treatment and their adherence

Treatment Concerns	Concerns/Questions	Do you have any concerns or unanswered questions about your medication? (explore the impact this has on self-management and confidence)
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Adherence and Persistence

3. Thinking about the treatment you have received, I want to explore how you follow or have followed your medication regimen. Many people have their own way of taking their medicines, which can be different from the instructions given by the doctors. What do you do / what is your routine?

Aim: to understand adherence and persistence to DMT

Prompts / sub questions

Clinical Framework	Topic	Detail
	Clarify	What is your current medication regimen?
Treatment Necessity / Treatment Efficacy / Motivation to Adhere	Persistence	Have you ever decided to stop using your medication? [If yes] - what made you do this / how long for? [If no] – what is it that makes / made you continue?
Treatment Necessity / Treatment Efficacy / Motivation to Adhere	Adherence	Do you follow your medication regimen as advised by HCP? Have you followed previous treatment regimens? (explore reasons for adherence or non-adherence as applicable)
	Adherence	To what extent do you follow the regimen?
Self-efficacy	Self-efficacy	Do you feel confident that you are able to follow the regimen? (explore reasons as applicable)
Treatment Necessity / Treatment Efficacy / Motivation to Adhere	Non-adherence: reason	When you haven't followed the regimen as prescribed, what are the reasons for this? Explore reason for non-adherence (current and previous) - <i>Change depending on how you feel? (e.g.</i>

		<i>side effects, emotional reasons, no MS symptoms)</i> <ul style="list-style-type: none"> - Change depending on what you are doing? (e.g. holiday) -
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Self-efficacy

Clinical Framework	Topic	Detail
Self-efficacy / Cognitive Decline & Forgetting	Self-management strategies	Do you have any strategies to help you remember? (i.e. planning, reminders)
Self-efficacy / Cognitive Decline & Forgetting	Ease of self-management	Do you find it relatively easy to rather difficult to self-manage your treatment regimen? (explore reasons)
Self-efficacy / Cognitive Decline & Forgetting	Support	Do you have help with your treatment for MS? <ul style="list-style-type: none"> - From friends and family - Other support?

Self-management

Clinical Framework	Topic	Detail
Practical Barriers: Cognitive Functioning Motivation: Self-management	Self-management strategies	Would you develop any strategies to help you attend to your monitoring? (i.e. planning, reminders)
Practical Barriers: Cognitive Functioning Motivation: Self-management	Ease of self-management	Would you find it relatively easy or rather difficult to self-manage compared to your current regimen?
Practical	Independent	Do you think you would want help with your

Barriers: Cognitive Functioning	management / Support	monitoring regimen or would you manage it yourself? If you were going to have help who would you ask? <ul style="list-style-type: none"> • Friends and family? • Healthcare team? • Other?
Motivation: Self-management		

HCP interaction

4. I'd now like to talk to you about your experiences with healthcare professionals who are involved in the treatment and management of your multiple sclerosis. Can you tell me a bit about your interactions with your doctors and nurses?

Aim: To explore the possible impact of HCP interactions and support on adherence

Prompts / sub questions

Clinical Framework	Topic	Detail
	Who is the HCP? (Background)	Without giving their personal names, which HCPs do you see in relation to your multiple sclerosis? (e.g. GP, specialist, nurse, pharmacist, other)?
Treatment Necessity / Treatment Concerns	HCP understanding	Do you feel confident that your HCP understands your experiences with your Multiple Sclerosis and your treatment?
Treatment Necessity / Treatment Concerns	Confidence in HCP	Would you feel comfortable talking to your HCP about problems or concerns you had relating to your treatment?
Self-efficacy	Monitoring assistance	Does your HCP tell or support you with how to follow the medication regimen? Would you feel confident / able to talk to your HCP about changes you had made to your treatment regime?

Support

5. We are trying to understand what type of support has been helpful for people with multiple sclerosis. Have you ever accessed a patient support programme to help with your MS?

Aim: To explore current access to patients support and investigate what has been helpful, what has not and why?

Prompts / sub questions

Topic	Detail
Patient support	Have you ever accessed a patient support programme to help with your MS or managing your treatment for MS? Yes: What treatment was it for? What did it involve? Did you / do you find it helpful?
Current support	Do you currently access a support program or group? (e.g. web forum, advocacy group)
Use/Best	What kind of support have you found most useful/best?
Not useful/Helpful	What have you not found useful or helpful?
Gaps	Currently any gaps in the support you receive or have previously received?
Would you use additional support?	Is additional support something you would use/find appealing? - Yes: Why? - No: Why?

Thank you and Conclude

Thank you very much for talking with me today. The information you've given us will be very valuable.

Thinking back to what we have discussed, is there anything else that you would like to add?

Just before we go I wanted to say that we understand it can be quite tiring to talk about these types of things in depth, so don't be surprised if you feel a little tired, or you find



yourself thinking about some of the things that we have talked about. If you do feel as if you would like to talk about anything that we have discussed more, it can be a good idea to talk to someone with some expertise in this area – perhaps your GP or a member of the team at your hospital / clinic

Once again, thank you very much for taking the time to speak with us.

Appendix I Text if a Patient Respondent Raises an Adverse Event

[Safety Information is identified and the participant is on a Genzyme/Sanofi Product]

What you [have just said] / [said earlier in the interview] is classified as safety information (NOTE: follow the definition of Safety Information as per SOP). The product manufacturer commissioning this programme (Genzyme) is required to collect this kind of information in order to continue identifying new side effects, and ways in which the risks of known side effects can be minimised. Every report they receive contains potentially useful information. I would like to spend a couple of minutes with you now to collect the necessary details of this safety information, so that the manufacturer can fulfil their obligations. Are you willing to assist with the reporting of this?

If NO: Because I have become aware of this reportable safety information, I am obliged to report this to product manufacturer. I will file this report without identifying your personal details. I may use your initials, gender or age group in case follow-up is required and I need to contact you for this. I would also recommend that you speak to your doctor so that they are aware of what you have experienced, and if necessary, follow up with you.

If YES: Thank you. The information you provide will be sent Genzyme’s Drug Safety department who, although unlikely, may wish to contact your doctor for further information. Would you like to provide the name of your doctor and allow permission to share your full name to enable them to identify yourself to your doctor?”

[Allow the patient to respond –Address any question they may have regarding the safety information report]

If the patient agrees to their personal details being included in the report, their contact details and HCP details are sent with the report.

If the patient prefers not to share their details, the report is sent de-identified and as agreed per the Safety Information Reporting SOP.

“Thank you. The information you provide will be sent to Genzyme’s Drug Safety department.

[Safety Information is identified and the participant is on a NON-Genzyme/Sanofi Product]

What you [have just said] / [said earlier in the interview] is classified as safety information and we would therefore advise that you speak to your doctor so that they are aware of what you have experienced, and if necessary, follow up with you. *[Allow the patient to respond –Address any question they may have regarding the reporting of the safety information]*

Appendix II AE SOP

[Genzyme SOP has been superseded by Sanofi's SOP. Copy in gallery for information]

Appendix vii – Correspondence from the Chair of the HAS Faculty Research Ethics Committee

From: Julie Woodley
Sent: 30 April 2018 14:01
To: Helen Jackson <Helen.Jackson@uwe.ac.uk>
Subject: RE: Evidence of independent approval of MS research

Hi Helen

We have gone through our records as far back as 2010 and there is no record of Clare putting in an application. Don't suppose she has changed her name has she?
I have read through the protocol and I would have expected this type of study to have gone through FREC at the time. She could either have applied through FREC or the system she went through looks pretty robust so she could have submitted that evidence and we would have ratified the approval (This sometimes happens when people transfer and have approvals already in place.)

There is clear evidence of review and also that ethical principles have been adhered to but it should have come to a FREC

Hope that helps

Julie

Dr Julie Woodley
Senior Lecturer -Allied Health
Chair of HAS Faculty Research Ethics Committee
Rm 2K01 Glenside campus UWE
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Stapleton
Bristol BS16 1DD
+44 (0)117 3288528
UREC Research Ethics Website <http://www1.uwe.ac.uk/research/researchethics>

Appendix viii – Data extraction framework example

AutoSave OFF | Data extraction framework — Saved to my Mac | Search Sheet

Home | Insert | Draw | Page Layout | Formulas | Data | Review | View | Share | Comments

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B3 | fx | Identity / Symptoms

	A	B	C	D	E	F	G	H	I	J
1	Case (country and #)	Perception	Extract	Additional codes / notes						
2	ESPO5	Personal Control	The truth is I try to control it, I did not let the disease dominate me	Conflict						
3	ESPO5	Identity / Symptoms	Right now, the truth is that I do not notice symptoms as such, you're more tired but I've always been clumsy							
4	DE01	Personal Control	I think I cannot control the complete MS, you can only control something if you know where it comes from, at the beginning it is a mental and psychological burden to cope with	Emotional burden						
5	DE01	Consequences	I think, that I am excluded from many activities that I could have done before I got my disease. But I am looking for other activities which are feasible	Social exclusion / adapting						
6	DE02	Personal and treatment control	Through the medication I can [control MS], I would say, because the medication I am currently taking, since I use this medicine, I must say, it's so good to me, how I was with still no other medication							
7	DE08	Consequences	So for me, I can only hope that the disease will not deteriorate and apart from that I hope that the research methods are getting better and therefore the course of the disease will be more positive	Future experience						
8	UK08	Identity / Symptoms	The main problems I have with the multiple sclerosis are balance issues and problems with my left leg. I reached the point where I couldn't walk, at all, at one stage but on the treatment I am now able to walk short distances	Treatment efficacy						
9	UK08	Coherence / Knowledge	To be honest with you, I didn't really know much about multiple sclerosis so I was quite upbeat at the time because I really was unsure what it meant to me and what the future meant. So at the time, I was quite upbeat and happy to be honest	Impact / symptoms / early stages / emotional impact						

MS Experience | **Illness Perceptions** | Treatment Experience | Treatment Beliefs | Adherence | Self-efficacy | Self-management | Experience with HCPs & System | Social Support | +

120%

AutoSave OFF | Data extraction framework | Search Sheet

Home | Insert | Draw | Page Layout | Formulas | Data | Review | View | Share | Comments

Calibri (Body) | 12 | Wrap Text | General | Conditional Formatting | Format as Table | Cell Styles | Insert | Delete | Format | Sort & Filter

	A	B	C	D	E	F	G	H	I	J
1	Case (country and #)	Belief	Extract	Additional codes / notes						
2	UK02	Concerns	he said I really think you should go on a disease modifying drug, you know, and try to slow this progression now. And for a while I didn't want to, I was a bit unsure, because it was injecting, it was the Rebif and it was injecting	Treatment burden / injections						
3	DE04	Efficacy	I was surprised, when I got informed that Betaferon is not effective for everybody...and it was surprising. That I am the one out of the 30% where the drug is effective...I believe this helps me and so I'll continue to inject betaferon							
4	UK07	Necessity	I do just sometimes think I wonder what would happen if I didn't take it? But I don't think I would like to take the risk and see what would happen.	Risk of not taking						
5	UK07	Efficacy	Effective to me means, because I had changes in my scan within six months, when I had first got diagnosed they were saying the lesions had got smaller and there was no new activity in my brain. So that was a really big deal to me	Objective measure of efficacy (though still wants a break, see previous quote)						
6	UK03	Necessity	It makes me think well, what is the point? If I didn't inject, would it just be the same anyway? Because I find it hard when it is not a cure, it is not a thing that makes you feel better, it just makes you feel rubbish, gives you a headache	Testing medicine / no evidence / side effects						
7	ESPO1	Necessity	It is very important for me. It is very rare that I forget it. I am not obsessed with that, I do it automatically. That I know I need it, so for me it is important, and I can live with that	Routine to remember linked to perceived importance						

MS Experience | Illness Perceptions | Treatment Experience | **Treatment Beliefs** | Adherence | Self-efficacy | Self-management | Experience with HCPs & System | Social Supp | +

Ready | 120%

Appendix ix – examples of qualitative cases

	A	B	C	D	E	F	G	H	I	J
	Case (country and #)	Main code	Extract	Supporting Code(s)	How does this contribute to the code / theme?					
1	UK07	Treatment Necessity	I do just sometimes think I wonder what would happen if I didn't take it?	Testing medicine	People question the need and have doubts about medicine even when they still adhere (see next quote)					
2	UK07	Treatment Necessity	but I don't think I would like to take the risk and see what would happen.	Risk of not taking treatment	People are unwilling to take the risk of stopping treatment, even when they doubt it - link to seriousness of		Treatment Necessity Summary Treatment importance does appear to drive adherence behaviours, but people can still question the need for treatment but adhere. Symptom experience can drive need as well as reflections on past and potential future states.			
3	UK03	Treatment Necessity	It makes me think well, what is the point? If I didn't inject, would it just be the same anyway? Because I find it hard when it is not a cure, it is not a thing that makes you feel better, it just makes you feel rubbish, gives you a headache	Testing medicine / Side effects	People question the need and have doubts about medicine, linked to not being a cure / no immediate benefit					
4	ESP01	Treatment Necessity	It is very important for me. It is very rare that I forget it. I am not obsessed with that, I do it automatically. That I know I need it, so for me it is important, and I can live with that	Drivers of adherence / Routines	Necessity / importance drives adherence - becomes part of routine					
5	UK04	Treatment Necessity	sometimes I feel like I am on this medicine and I don't know why I am on it...obviously I understand that, you know, I have got these changes in my MRI but because I am well, in myself, sometimes I feel like a bit of a fraud	Symptom experience	Experience of symptoms (overt) drives need for treatment					
6	ESP04	Treatment Necessity	especially because I don't want to feel worse. Now I have a normal life, more or less. I don't want to feel worse and end up in a wheelchair	Drivers of adherence	Fear of future drives need for treatment					
7	UK05	Treatment Necessity	it's not that I don't want to feel worse, it's that I don't want to feel worse and end up in a wheelchair	Drivers of adherence	Fear of future drives need for treatment					

Microsoft Excel ribbon: Home, Insert, Draw, Page Layout, Formulas, Data, Review, View, Shape Format. Includes font settings (Calibri, 11), alignment options, and table formatting tools.

	A	B	C	D	E	F	G	H
1	Case (country and #)	Main code	Extract	Supporting Code(s)	How does this contribute to the code / theme?			
2	UK07	Testing medicine	I do just sometimes think I wonder what would happen if I didn't take it?	Treatment Necessity	People want to test the efficacy / impact of medicine for themselves by stopping / having a break		<p>Testing Medicine Summary</p> <p>The 'urge' to be able to objectively know if treatment is working seems to be important for some people. This can be driven by dislike of the treatment but also just when treatment impact is not overt / believed</p>	
3	UK03	Testing medicine	it makes me think well, what is the point? If I didn't inject, would it just be the same anyway? Because I find it hard when it is not a cure, it is not a thing that makes you feel better, it just makes you feel rubbish, gives you a headache	Treatment Necessity	People want to test the efficacy / impact of medicine for themselves by stopping / having a break			
4	ESP02	Testing medicine	I have stopped, when I feel bad about the effects to see, to see if it is helping	Drivers of non-adherence / Side effects	Side effects drive people to question if treatment is working / worth it			
5	UK08	Testing medicine	I get tired of the injections, they make me fed up and I wish I could tell for sure it was helping, but then I am too scared to stop	Treatment Burden	Injection fatigue drives people to question if treatment is working / worth it			
6								
7								
8								
9								