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The role of information in therapeutic decision-making for adults living with Multiple Sclerosis (MS)

A thesis submitted to Imperial College London for the Degree of Doctor of Philosophy

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Declaration of Originality

This thesis is an original work and all other references that are not my own have been referenced to the original authors and/or publishers. I am referred to henceforth as 'thesis author' to indicate work attributed to myself.

Copyright Declaration

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Publications

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Oral presentations

Wilkie D. Managing decisional conflict in MS – a question of evidence or psychology? Hamburg, Germany. SIG conference. Nov 2015.

Wilkie D. Understanding the role of decision conflict in making choices about DMTs in MS. Milan, Italy. SIG conference. 16-17 Nov, 2017.

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Abstracts & Poster presentations

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Dedication

"Logic will get you from A to B.
Imagination will take you everywhere."

Albert Einstein

Abstract

Background: People with MS (pwMS) are confronted with 16 therapies. These come with risks that have led to drug withdrawals and changes to prescribing regulations. Patient autonomy is seen as desirable and has challenged the role of the health care professional (HCP). Greater scrutiny of the decisional process is necessary to determine if complex decision-making can be influenced.

Methods:

i) Attendees to an MS conference (n=105) and a cohort of patients on treatment (n=76) were contacted about their current treatment status and if they had decisional conflict (DC).

ii) Prospective study (n=73) of pwMS offered treatment, used instruments to map pwMS through their decision post-consultation.

iii) Results informed a film aimed at pwMS (n=1001) and a comparator group without MS (n=148). Participants reviewed the film with the primary aim of measuring understanding of the concepts portrayed.

Results:

i) Data from the cohorts in methods i-ii (n=254) were compared. The treatment status 'not satisfied' was present in 113/254 (44%) and 135/254 (53%) had DC.

ii) DC was significantly increased in a treatment naïve subgroup 75% (27/36), p=0.013.

iii) In the 'offered treatment' study, making a treatment decision took a mean of 29 days (range 0-308). Multivariate regression analysis found those with less confidence in their healthcare decision-making were more likely to have DC (n=72, SURE scale; adjusted R^2 0.11, p=0.02; SURE-subscale adjusted R^2 0.04 p=0.04; DCG adjusted R^2 0.04 p=0.04).

iv) The neurologist perceived significantly more consensus during the consultation (39.24±6.54) than pwMS (31.22±10.64; p<0.001). A multivariate regression analysis found that shared decision making (SDM) was associated with lower DC alongside patient engagement (n=67, adjusted R^2 0.382; p<0.001).

v) There was a high level of film understanding in the total population (85%).

vi) A multivariate regression analysis found that 'education' was associated with film 'understanding' (n=892, adjusted R^2 0.023, p=0.000). This meant having less education was associated with increased understanding. A one point increase in education was associated with a .170 reduction in understanding.

Conclusions:

i) PwMS have high levels of DC when making treatment decisions.

ii) Low engagement is associated with increased DC but an HCP consultation with good SDM is associated with lower DC.

iii) A film produced a high level of understanding in both MS and non-MS populations. Those less educated had the highest understanding overall.

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Thesis Formatting

The following content follows Imperial College London formatting guidelines. Text is double-spaced (size 12) with the exception of tables and figure legends that follow size 10 and 1.5 spacing. References are in Harvard style with the exception of Table 8 References which follows the Vancouver formatting style.

Glossary of Terms and Abbreviations

AE	Adverse Event
API	Autonomy Preference Index
BIT	Behavioural Insights Team
CBT	Cognitive Behavioural Therapy
CCG	Clinical Commissioning Group
CCSVI	Chronic Cerebro-Spinal Venous Insufficiency
CG	Control Group
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
CPS	Control Preference Scale
DA	Decision/Decisional Aid(s)
DAS-O	Decision Analysis for Oncology
DC	Decisional Conflict
DCG	Decisional Conflict Gauge
DCS	Decisional Conflict Scale
D-DCS	Dyadic Decisional Conflict Scale
DMT	Disease Modifying Therapy/Therapies/Treatments
DR	Decisional Regret

DRS	Decisional Regret Scale
DSAT	Decision Support Analysis Tool (DSAT)
Dx	Diagnosis
EBPI	Evidence Based Patient Information
EBSIMS	Evidence-Based Self-Management in MS relapses
EDSS	Expanded Disability Severity Scale
EMA	European Medicines Agency
EUT	Expanded Utility Theory
GDPR	General Data Protection Regulations
GMC	General Medical Council
GP	General Practitioner
GSE	General Self Efficacy Scale
HADS	Hospital Anxiety and Depression Scale
HAQUAMS	Hamburg Quality of Life Questionnaire in MS
HCEQ	Health Care Empowerment Questionnaire
HCP	Health Care Professional
IA	Information Aid
ICC	Intraclass Correlation Coefficient
ICF	Informed Consent Form
IG	Intervention Group

IMP	Investigational Medicinal Product
IP	Interprofessional
IPS	Influential Parties Scale
ISDIMS	Informed Shared Decision-making about Immunotherapy for patients with Multiple Sclerosis
JCV	John Cunningham Virus
MAGIC	Making Good Decisions in Collaboration
MAPPIN'SDM	Multifocal Approach to Sharing in Shared Decision Making
MHRA	Medicines & Healthcare Products Regulatory Agency
MRC	Medical Research Council
MS	Multiple Sclerosis
MS-DOUBT	Decisions Of Uncertainly Broaching Therapies in MS
MSTC	Multiple Sclerosis Trials Collaboration
MSTKS	MS Treatment Knowledge Scale
NHS	National Health Service
OPTION	Observing Patient Involvement In Decision Making
PABS	Patient Attitudes and Beliefs Scale
PAM	Patient Activation Measurement
PBMS	Planned Behaviour in MS decision making in DMTs
PDPAI	Provider Decision Process Assessment Instrument

PICS	Perceived Involvement in Care Scale
PIS	Patient Information Sheet
PML	Progressive Multifocal Leukoencephalopathy
PPI	Patient Public Involvement
PPMS	Primary Progressive Multiple Sclerosis
PRC-REMS	Patient Research Cohort – Rapidly Evolving Multiple Sclerosis
pwMS	People with Multiple Sclerosis
QoL	Quality of Life
RCT	Randomised Controlled Trial
RIKNO	Risk Knowledge in Relapsing Multiple Sclerosis
RIMS	Rehabilitation In Multiple Sclerosis
RMS	Relapsing Multiple Sclerosis
RPAD	Rochester Participatory Decision Making Scale
RRMS	Relapsing-Remitting Multiple Sclerosis
SDM	Shared Decision Making
SDM-Q-9/Doc	The 9-item Shared Decision Making Questionnaire/ Doctor's version
SF-36	Short Form 36 Health Survey
SPMS	Secondary Progressive Multiple Sclerosis
SURE	Sure of Myself, Understand Information, Risk-Benefit Ratio, Encouragement

TPB-S	Theory of Planned Behaviour Scale
TEIQue	Trait Emotional Intelligence Questionnaire
TFS	Treatment Factors Scale

Chapter 1 Introduction

1.1 Positioning of the research

The prognosis for patients with Multiple Sclerosis (MS) varies widely and remains unpredictable. Disease-modifying treatments (DMTs) have become available for people living with relapsing forms of the disease which in general occurs early in the disease course (Lugaresi et al., 2013), but until recent breakthroughs with Ocrelizumab and other treatments at various stages of development (Baldassari and Fox, 2018), (Ciotti and Cross, 2018), (MS_Trust, 2019c), effective treatment for more progressive forms of the disease (i.e. when clinical relapses are absent or are not the most relevant clinical manifestation) has remained elusive (Fox et al., 2012).

Balanced against an uncertainty of outcome is that treatment should probably be considered soon after diagnosis, as neurologic damage occurs early on in the disease course and there is growing evidence to suggest that early intervention is important (Kira, 2008), (Kappos et al., 2007), (Elovaara, 2011), (Montalban et al., 2018). People with MS may therefore need to consider a therapy in the absence of any on-going symptoms (Kennedy, 2013) in order to prevent or delay future damage. Psycho-pathological disturbance has been seen to affect some people with MS even at onset, which can have further implications on quality of life to treatment adherence (Haussleiter et al., 2009).

Licensed treatments vary from a route of administration standpoint, ranging from injectables (eg. range of beta-interferons and copaxone), infusions (eg. natalizumab, alemtuzumab) to oral treatments (eg. fingolimod, dimethyl fumarate, teriflunomide).

There are further treatments being tested as part of clinical trials in relapsing MS (ponesimod, evobrutinib, ublituximub, diroximel fumarate) and progressive MS (idudilast, masitinib, etc) (MS_Trust, 2019a).

Treatments have side effects ranging from common and mild with beta-interferons (e.g. injection site reactions) to rare but severe (death from Progressive Multifocal Leukoencephalopathy (PML) with natalizumab). PML is an opportunistic infection that is derived from the presence of the John Cunningham Virus (JCV) in immune-suppressed individuals [ie. those on DMTs]. The prognosis of PML can be devastating including motor dysfunction, loss of vision and dementia (Warnke et al., 2010). A major consequence of these side effects is that people refrain from staying on treatments longer-term, although the side effects can be mild (Nicholas et al., 2011).

Decision-making is complicated by a growing range of treatments so it is essential that people living with MS are fully aware of their options - married to risk - in order to make an informed choice. This scenario has highlighted the need for evidence-based medicine which has been described as a combination of the best external evidence (eg. systematic reviews) with that of clinical expertise and patient choice (Sackett et al., 1996). This approach suggests a level of pro-activity on the part of physician and patient in order for it to work and thus, how the information is best presented and communicated is one research objective of this review. In addition, the preferred role and risk knowledge of the patient and how these can be measured are pivotal.

Patient autonomy has been defined as the right of self-determination when considering a health matter (Heesen et al., 2013). In a German study, 80% of MS patients were

found to favour an active role in decisions surrounding treatments and were understanding of complex information. Despite this, an assessment of risk knowledge averaged 34% across 56 participants in a pre-study focus group. Of interest, the highest knowledge of risk was reflected in those diagnosed within a year (Heesen et al., 2007).

In the UK, patient decision-making is highlighted in the National Health Service's (NHS) Constitution (2009) which outlines the patient's right to be engaged in decisions surrounding their own care and access to information in support incorporating alternative treatments and potential risks (NHS, 2009). Decision-making as part of good clinical practice and duty of care for doctors is guided by the General Medical Council (GMC) in publications including end of life (GMC, 2010).

The White Paper, 'Equity and Excellence: Liberating the NHS' provided a template of the then Government's agenda of an NHS that prioritises patient engagement where 'no decision about me, without me' is the preference. Recommendations included giving people greater input over their healthcare and treatment, enabling them to make informed choices and ultimately to improve health outcomes (DOH, 2010).

Following consultations with local authorities, voluntary and NHS groups, patient representatives and others, a follow-up consensus emerged as detailed in the follow-up report (DOH, 2012), acknowledging the need for shared decision making (SDM) and providing the information and support required for self-management of their own condition. One outcome of this commitment is the creation of The Right Care Shared Decision Making Programme. The programme is just one example of expanding

government aims to embed SDM into NHS practice. As such, the intention to create 37 Patient Decision Aids (PDA) was established, including one for MS (NHS, 2013).

As the patient-physician relationship has evolved, the consideration of SDM has become more commonplace. SDM in the context of healthcare, is defined by Charles et al (1997) as:

(1) 'involving at least two participants (physician and patient);

(2) that both parties share information;

(3) that both parties take steps to build a consensus about the preferred treatment; *and*

(4) that an agreement is reached on the treatment to implement'

(Charles et al., 1997).

SDM has been further defined as a process in which patients and HCPs work in tandem to clarify and select treatments, tests and interventions, on-going self-management or support goals ideally based upon clinical evidence and the patient's own preferences which are well informed. It involves the provision of evidence-based information about the options available incorporating risk factors, potential outcomes and uncertainties, with the necessary support and counseling as part of a system for establishing, managing and implementing patients' informed preferences (Coulter and Collins, 2011).

SDM provides an area of focus for the clinical environment but external influence may also play a role in treatment decisions.

With the aid of the Internet, patients are now in the position to enter a consultation with their physician armed with both preferences and knowledge, although accuracy of the latter may vary (Gerber and Eiser, 2001). The Internet, by its nature an organic entity where people can contribute information in the absence of evidence-based knowledge, can be erroneous and potentially influential.

Some patients have explored unproven therapies with limited or no scientific evidence (Berglund, 2012). One example is Chronic Cerebrospinal Venous Insufficiency (CCSVI), purported as a possible determinent of MS (Pullman et al., 2013). The news of the breakthrough spread via the Internet, leading hundreds globally to seek out the treatment, referred to as venoplasty, which involves the insertion of an inflated balloon into a blood vessel to remove a blockage (Walker, 2011). Some have experienced complications from the procedure (Burton et al., 2011). The case of CCSVI highlights the urgent need to better understand how information is presented, absorbed and interpreted by individuals *outside* of the clinical setting.

Pullman et al (2013) looked at Canadian coverage of the CCSVI study acknowledging that social media helped permeate political spheres partly because of the rapid spread of information (which was arguably misinformed), but also with its ability to assemble many people, ultimately priming political leaders to act. The most powerful and persuasive 'evidence' to public and patients happened to be anecdotal (Pullman et al., 2013), (Riise, 2012).

Against this backdrop, people with MS need to make decisions but, as yet, the process to influence decision-making is unclear. As described, the involvement of the Internet

and social media in coalescing people to drive for democratic change and central control, implies it can affect macro decision-making (Dutton, 2009). In particular its influence on how health-care decisions are made is not known. It has been proposed that HCPs need to engage with the public through this medium but how this may be achieved optimally is unclear.

1.2 Search strategy

The aim of the following literature review was to consider some of the key areas described in chapter 1.1 in line with the research objectives, mainly:

- Understand the role of decision-making for MS patients considering treatment options.
- Investigate the relationship of image and narrative and how it is presented and its effects on decision-making.
- Identify different streams of information and how presentation is absorbed and interpreted by individuals.
- To determine if decision-making can be influenced with reference to treatment choice.

A search up to May 2019 was conducted with no limit on a start date with notable reference to decision theory, which has a substantial history. MS-specific research with reference to treatment choice was limited to the last 25 years (1994-2019) to reflect the MS treatments that have emerged over this period. Where possible, the latest Cochrane Reviews have been consulted (including unpublished material) with

reference to decisional interventions. The search was limited to words within the subject, abstract or heading using the following key words or terms: “decision making”, “decision aids”, “risk”, “treatment”, “shared decision making”, etc. These were combined utilising Boolean logic (AND being the preference over OR) with keyword ‘‘multiple sclerosis’’ employed to gain a more accurate reflection of current research specific to the disease. From the search process, other papers of relevance by method of snowball effect were accessed (from paper reference lists, search engine recommendations). Initial relevance of papers was conducted with reference to abstracts, conclusions and key authors (Elwyn, Heesen, Kasper, Kopke, Solari, etc) in the field of decision-making.

Sources included databases: Ovid (Medline), Science Direct, Google Scholar, PubMed, Wiley Online Library, Cochrane Collaboration as well as psychology databases incorporating behavioural and social sciences (Taylor & Francis, JSTOR).

Before the process can be considered in greater detail, it is essential to further define MS as a disease.

1.3 MS: Characteristics of the disease

MS is a chronic inflammatory autoimmune disease of the central nervous system (CNS) with a variable disease course and no cure. Symptom onset usually occurs in young adulthood and affects women more than men (Mackenzie et al., 2013). The cause of MS has yet to be established but has been linked to an interaction between environmental and genetic factors (Compston and Coles, 2002).

MS presents in three main ways: the most common form is relapsing-remitting MS (RRMS), followed by secondary progressive MS (SPMS) and primary progressive MS (PPMS) (Loma and Heyman, 2011). Clinically isolated syndrome (CIS) is characterised by 'a single attack of neurological symptoms caused by inflammation or demyelination' which may or may not lead to MS (Kennedy, 2013). SPMS follows on from RRMS and is characterised by permanent neurological damage (Palace, 2003).

The Mcdonald criteria, which guides clinicians in the diagnosis of MS, published further recommendations in 2017 for those with CIS. On the basis of clinical presentation featuring evidence of one attack/relapse and evidence of one lesion on MRI, a diagnosis can be made if additional criteria is fulfilled: $\geq$1 lesion as detected by MRI or an additional relapse showing dissemination in time as demonstrated by the presence of oligoclonal bands or additional, new lesions since a previous MRI scan or evidence of a further attack/relapse occurring (MS_Trust, 2018a).

As DMTs have been proven to limit or slow down neurological damage, there is a rationale in starting treatment in the RRMS phase sooner rather than later. Theoretically people may need to consider treatment at the CIS level before the disease has been diagnosed and thus exposed to risks that were avoidable if an MS diagnosis is not confirmed.

Treatment efficacy varies per disease course and by individual and can come with considerable risk, as the next section describes.

1.3.1 Treatment Concerns

Whilst the relapsing form of the disease is better served than ever before, there is an absence of effective treatment for those living with progressive MS beyond symptomatic interventions which include Fampridine, prescribed for improving walking speed. Some drugs have shown promise tested as part of clinical trials. Examples include high-dose simvastatin tested in a UK phase II study from which the results have been published, showing a reduction in the annualised rate of whole-brain atrophy versus placebo (Chataway et al., 2014). The results are now being tested in a larger, phase III study (STAT-2) in people living with SPMS (Williams et al., 2019).

However, a study looking at reducing brain atrophy utilising four treatment arms (amiloride, fluoxetine, riluzole, or placebo) in SPMS failed (National MS Society, 2018), as did studies looking at Natalizumab in SPMS, although some improvement was seen in upper limb function (Kapoor et al., 2018), and which is now getting greater focus in progressive MS as a viable outcome measure (Pisa et al., 2020).

Siponimod in SPMS is a promising treatment (Kappos et al., 2018). The OPERA I and II trials successfully showed relapse reduction comparing ocrelizumab with interferon beta-1a in relapsing MS, and demonstrated a decrease in relapse rates measured annually (Hauser et al., 2017). Notably, ocrelizumab is the first drug to lower rates of clinical and MRI-evidenced progression in patients with PPMS and can now be prescribed in England. The phase III trial (ORATORIO) in patients with

PPMS confirmed disability progression was significantly lower in the active treatment group versus placebo (Mulero et al., 2018).

Cost married to efficacy as well as safety, remain key areas of concern in MS treatment (Ali et al., 2013). It is essential to detail the process as MS treatments continue to emerge at different stages of development and the drug portfolio is likely to increase.

Author Rice (2013) highlights the need to weigh the comparative safety of older treatments such as interferons against newer biological agents that display higher efficacy (alemtuzumab, natalizumab) but which come with greater risk of complication (Rice, 2013). Authors Ali, Nicholas & Muraro (2013) have visualized these risks in figure. 1, adapted by Wilkie (2019) to reflect treatment access.

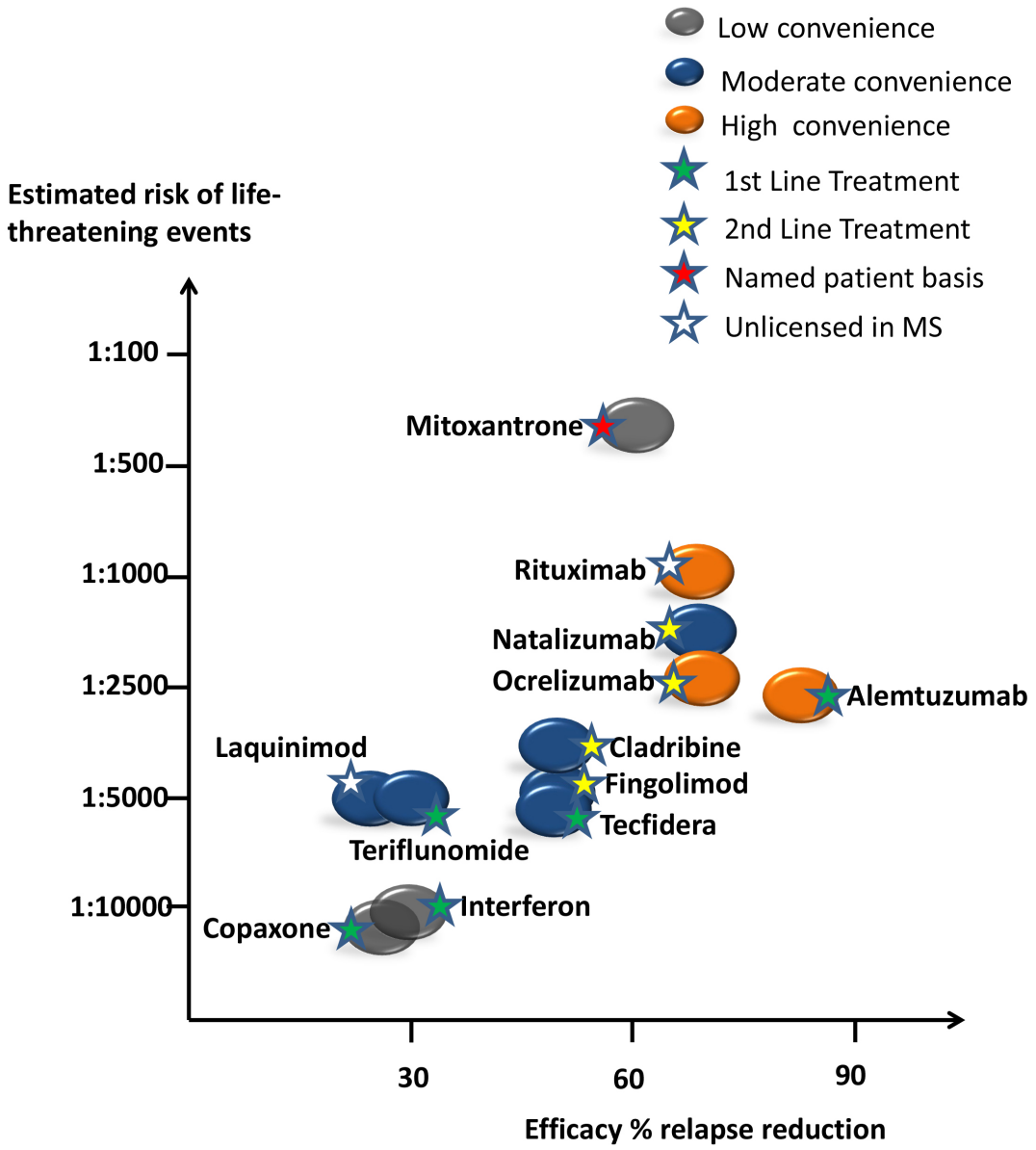

Figure 1: 'Efficacy of relapse reduction versus estimated risk of life threatening AEs of drugs, both licensed & in-phase 2/3 development of MS, indicating the degree of convenience of admin' (Ali, Muraro & Nicholas, 2013:p.644) adapted by Wilkie

Additionally, there are practical considerations for both the patient and healthcare team. Convenience in this context is defined by frequency of administration (daily, weekly, monthly) and type of administration e.g oral, infusion) (Higgins et al., 2014).

As an example, fingolimod must be initiated over a six-hour period due to cardiac concerns but any initial inconvenience is offset by the convenience of taking an oral tablet once daily if safety monitoring is passed. As figure. 1 indicates, natalizumab comes with higher efficacy but comes with moderate inconvenience in the form of monthly infusions. There are therefore practical considerations for patients, the staff administering as well as cost implications to the NHS Trust which, if significant, could lead to waiting lists. During this time, patients may need to consider alternative treatment options or/and risk deterioration in their health status if delayed. The need for consensus on the spectrum of treatments available has led to the publication of guidelines (Montalban et al., 2018). This is a working document that will need updating over time, as well as for established drugs as their safety profiles continue to develop. One example is Alemtuzumab, which the European Medicines Agency (EMA) investigated following cases of stroke connected to the drug (Durand-Dubief et al., 2020). Its use is now restricted to rapidly evolving severe MS following a safety review (MS_Trust, 2019b).

There are additional factors in that certain drugs (fingolimod, natalizumab) are second-line treatments (although in the UK natalizumab can be prescribed as a first line treatment if a person presents with highly active MS). A person may therefore need to fail a first-line treatment before being considered for a second-line treatment.

Decisional Conflict (DC) may occur when there is uncertainty about the action to take. This is especially apparent in situations involving risk or outcomes that are uncertain. Such a choice might be high stake weighing potential losses or gains. Social and

cognitive factors may also intensify the uncertainty (O'Connor, 1993 (updated 2010)). Experience of patients on a treatment eg. natalizumab, has been measured against other DMTs.

A review carried out by Tur et al. (2013) found that risk acceptance was associated with personality, but was also dependent on personal circumstance eg. being JCV positive but at low risk of developing PML. Those most accepting of risk were people on natalizumab compared with those on first line treatments. It was also found that those with high scores of neuroticism (anxious traits) were willing to take higher risks. Generally those presenting with aggressive MS were not greater risk takers, going against the expectation of the authors (Tur et al., 2013). These are noteworthy findings, suggesting that decision-making in individuals can't be generalised by group and a more personalised approach may be warranted, depending on the time-point in a person's disease course and treatment history. In addition, the physician's own view may be influential, as indicated by a study from the same group.

Tur et al (2012) looked at treatment discontinuation in those on natalizumab referencing PML risk and found that the physician's role was pivotal. Testing positive (and to what degree) for JCV was influential, though the physician's own position (and presumably how this was interpreted by the patient and associated party of relatives) also appeared to play a part. The authors acknowledge that this observation was not accounted for in the process, thus the individual neurologists' age and duration of

neurology experience alongside the patients' psychological profiles are missing from the analysis (Tur et al., 2012).

1.4 Accessing Treatment

In the UK, access to treatments on the National Health Service (NHS) is guided by the National Institute for Health and Care Excellence (NICE). Setup in 1999 as a specialist health authority, it is now a non-governmental departmental public body providing 'evidence-based guidance and advice for health, public health and social care practitioners' (NICE, 2013).

Licences are granted on the basis that high standards of safety and quality have been met and that it works for the application intended for use. Licencing is obtained through:

- The Medicines & Healthcare Products Regulatory Agency (MHRA) .
- The European Medicines Agency (EMA).
- NHS England (NHS in Wales, Northern Ireland and the Scottish Medicines Consortium oversee other parts of UK access to treatment in their respective Trusts) (NHSScotland, 2020), (MS_Trust, 2018c).

The MHRA is UK-specific (Gov.UK, 2020) whereas the EMA can grant licences within the European Union (EU) (EMA, 2020). The FDA is the equivalent in the US (Wikipedia, 2020c). Before a licence can be granted, the medicine needs to go through defined phases of development, commonly starting with a clinical trial enlisting

healthy volunteers (Phase I) before being trialed in hundreds of patients with the target disease (Phase II) and if safety and outcome measures are met, trialed in a larger number, typically thousands (Phase III). (NHSChoices, 2012).

Notably Phase IV trials can follow a drug's safety longer-term and post-licensing, to gauge risks such as side effects and adverse events (AEs) previously unknown as part of the limitations of a clinical trial. In addition, access to treatment varies. Despite a statutory obligation on the NHS to fund prescriptions, some MS patients have been denied treatment altogether (Hamann et al., 2007). Patients and practitioners must therefore stay up-to-date and manage expectation (Elovaara, 2011).

It is clear from this analysis that on one side there is a macro-environment which incorporates pharmaceutical companies who develop drugs, the regulatory bodies who look at a safety profile and cost of a drug and the NHS which provides the practical access for implementation and administration. On a micro-level, there is the patient and healthcare practitioner who must interpret this information with the aim of making an informed decision. Before this can be considered in more detail, it is important to define further what a decision is, in the context of healthcare and outside of it.

1.5 What is a decision?

1.5.1 A definition

The Oxford English Dictionary (Oxford, 2005) defines a decision as:

1. 'A choice or judgement made after considering something.
2. The action of deciding something.

3. The ability to decide things quickly.'

(p.190).

A decision is defined by the Cambridge Dictionary Online (2013) as follows:'a choice that you make about something after thinking about several possibilities' (Cambridge, 2013).

In the context of the wider environment incorporating healthcare, such a vague description is inadequate. Decision-making has been further defined as a *process* rather than an *act* based on multi-criteria. The process involves pre-decision, the decision itself, and post-decision. The pre-decision stage may incorporate a level of conflict, whereby options are considered out of dissatisfaction with the status quo, initially an objective process that may involve input from others, which, over time narrows into a subjective intention (the process). Finally the post-decision will incorporate a level of reflection which may include satisfaction or regret. The overall process is punctuated with a series of mini (or partial) decisions. (Zeleny and Cochrane, 1982).

1.6 Decision Theory

According to Milkman et al (2009), decisions create outcomes. Challenges to the process include too much information, time constraints and choices that must be made concurrently. In a global economy, such decisions can affect society as a whole. It is recommended that future research focuses on improvement strategies:

'seeking to answer the question: how can we improve decision making?' (Milkman et al., 2009).

Improved decision-making is discussed by Milkman et. al (2009) with reference to the workings of the mind, encapsulated as 'system one' and 'system two':

> 'System one refers to our intuitive system, which is typically fast, automatic, effortless, implicit, and emotional. System two refers to reasoning that is slower, conscious, effortful, explicit, and logical' (p.380).

People are more likely to employ system one thinking if they are lacking information, or have time and cost implications to consider, though it has been proven, depending on the environment and circumstance, that the immediacy of system one can be used effectively (Milkman et al., 2009). One application of this is in the variation on the theory, proposed by Dijksterhuis and Nordgren (2006). In their Theory of Unconscious-Thought, conscious thought (akin to system two) requires attention whereas unconscious thought (comparable to system one) is the opposite. They have demonstrated through experiments where people's responses are purposely hurried or delayed that when asked to make a decision based upon a number of alternatives, that simpler issues can be better addressed using conscious thought and more complex decisions with unconscious thought (Dijksterhuis and Nordgren, 2006).

In his book 'Blink', author Gladwell (2005) describes a process of unconscious thought called 'thin-slicing' whereby people are able to recognise patterns in behaviour despite limited exposure or experience of a situation. In experiments,

people have been able to accurately predict if a married couple later split based upon short video recordings, as well as make an assumption about the quality of a teacher based upon less than five seconds of footage supporting the views of students with extensive exposure to the same teacher (Gladwell, 2005).

It is argued by authors Milkman et al (2009) that for deeper decisions, the implications of system one (such as bias) must be better understood and, with improved strategies, this will lead to better decisions. It has been proposed that instead of switching people's mindset from system one to two (away from bias), it is instead easier to manipulate the environment in which they operate (Milkman et al., 2009).

Elwyn and Miron-Shatz (2010) have investigated what might constitute a good decision and how it might be measured. They have split the decision-making process into two categories: *Deliberation* and *Determination*. Deliberation covers the initial groundwork that leads to a decision eg. information search, imagining counter-scenarios, projection of outcomes and a preference for a way forward. The determination is the integration of these elements leading to a choice being made. They argue that no decision can be made without separating these two areas. One issue emerging from this process is at which time point should an outcome be measured? (Elwyn and Miron-Shatz, 2010). In MS, this can be demonstrated by the challenges facing randomised controlled trials (RCTs). By definition, an RCT is a study in which people with shared or similar characteristics are assigned to two or more groups to test a treatment. This can be against a control group receiving an alternative treatment or no treatment (NICE, 2014).

At which time-point to measure the success or failure of a healthcare intervention in this context is one concern. Hypothetically, a person's viewpoint of a treatment may differ greatly one month beyond commencing treatment with few complications, compared to three or six months post-intervention when other factors may have emerged that have altered their initial enthusiasm: risk factors such as AEs, issues of treatment convenience and other factors that were not initially present.

Fuzzy Trace Theory (FTT) is one theoretical framework that has been utilised in risk communication in a healthcare setting. FTT is based on assumptions that may exist in people's processing of memory and reason resulting in them getting the 'gist' of a scenario and to recall facts, but failing to grasp the underlying meaning (Krones et al., 2010). Decision interventions have been informed by FTT and evaluated in research (Armitage and Conner, 2001). One expression of this is in the form of numeracy and presentation. Bar graphs can convey relative risk and encourage risk-avoidance because individuals make a gist-based judgment by likening the heights of the bars (Stone et al., 2003) as cited by (Reyna, 2008).

The analytic hierarchy process (AHP) has been applied to healthcare decision making. AHP is a decision-making method for multiple-criteria decisions with conflicting objectives, in order to prioritise alternatives. This could manifest as a hierarchical structure that incorporates the goal, criteria, and possible alternatives. (Heesen et al., 2011). Figure 2 (over-page) shows this in-action in the context of eye surgery (Singpurwalla et al., 1999). An alternative application in MS could be represented as follows: *Goal* (eg. Fewer relapses), *Criteria* (eg. Cost implications of Chosen

Treatment, Safety Profile (incorporating AEs), Drug Route (eg. oral, subcutaneous, infused), Improved Quality of Life (QoL), Frequency of drug administration (daily, monthly, etc) and *Alternatives* (eg. Treatment 1, Treatment 2, No Treatment).

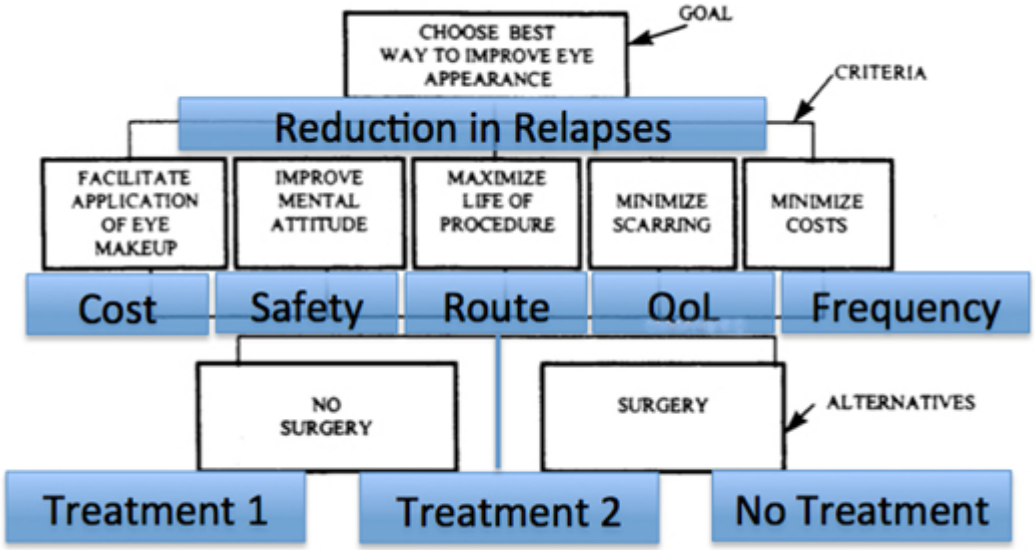

Figure 2: 'The hierarchy for cosmetic surgery of the eyelid' (Singpurwalla, Forman & Zalkind, 1999:p.281) adapted by Wilkie, showing how MS factors can be applied to the same model.

Decision theories can be split into two specialties, as follows: *normative* (how decisions should be made) and *descriptive* (how they are actually made). In this context, *normative* may be described as the 'prerequisite' of a decision (Hansson, 1994). It has been argued that descriptive theories (e.g. prospect theory) have been influenced from normative theories (Ajzen, 1991). One of the most cited examples of normative theory is Expected Utility Theory (EUT) and as part of descriptive theory, Regret Theory.

Regret theory proposes that people, when making decisions, consider the consequences of a chosen action, but at the same time alternative actions are compared. They are interdependent rather than independent. A person may therefore purchase insurance, because they foresee a bad outcome in the event of an accident. Alternatively, an individual may gamble a small amount of money, but regret not gambling bigger if the outcome is favourable (Ajzen, 1991).

If applied to MS, patients are faced with a future self married to expectations, but must also consider less favourable outcomes. Regret theory has also been proposed as a measure of a decisional intervention and will be returned to in the next section as part of a decision outcome.

EUT is based upon risk and uncertainty and is attributed to 18th century mathematician, Daniel Bernoulli (Barratt, 2008). In decision theory, traditionally the separate concepts of risk and uncertainty are not divided. Risk has been described as outcome measures that are known whereas under uncertainty they are not. Most decisions are realised between the two areas, hence the consolidation (Suhonen, 2007). EUT proposes a scenario of what a so-called 'reasonable' person will pay to enter into a gamble. The expectation was that it would be theoretically feasible to pay up to the anticipated value, but Bernoulli hypothesises instead that if a coin is flipped over-and-over until a head presents, using the equation \$2n, where n represents the number of throws to elicit a head, the expected pay-off is therefore infinite. Furthermore, Bernoulli stated that people would only pay a relative amount. Essentially the gamble

value (also known as 'utilities') is therefore not equal to the expected value (Starmer, 2000).

EUT has however been challenged. One issue with this theory is that its origins are in economics and as numbers are easier to predict than multi-layered decision-making by individuals, as is the case in healthcare, then its linear approach has limitations.

For this reason, non-expected EUT theory has emerged and one expression of this is the Allais paradox: essentially, people make decisions that violate mathematical equations and are often inconsistent. Building on this, authors Daniel Kahneman and Amos Tversky (1986) have observed that people's interpretation of risk differs between 0 and 1 or even 99 and 100. Although the difference is the same between both scenarios, people do not always think logically, notably in gambling scenarios: people will often gamble big, even if the odds are not as great as lesser bets. Often people won't consider the overall, bigger picture, beyond the moment. Generally speaking, people are more loss averting, meaning that potential losses are often the focus as opposed to gains. When patients were asked if they would choose surgery in a hypothetical emergency situation, the majority chose surgery when the survival rate was presented as 80% versus a presentation that cited death from the same intervention at 20%. Essentially, the odds were the same but the *framing* of the scenarios mattered (Michie et al., 2004); (Tversky and Kahneman, 1986).

In the context of healthcare, three stages of the decision making process have been identified referencing patient autonomy: prerequisites [or antecedent]; the process itself and the outcome. A prerequisite may include factors including personality, role

preference and risk knowledge; the process (patient-physician interaction, perceptions of uncertainty or DC) and the outcome encompassing outcomes, informed choice and matching role preference. (Heesen et al., 2013). This process is best illustrated as part of SDM.

1.7 Shared Decision Making (SDM)

It was established in the introduction a brief overview of what SDM incorporates and the growing importance of placing the patient at the centre of healthcare. Clinical application is vital, but as important is the conceptual models on which SDM is based. This sub-chapter considers some of these models.

SDM has evolved to incorporate not just the viewpoint of the patient, but that of the physician (or healthcare practitioner) as part of a *dyadic* process where decisions are reached in tandem (Légaré et al., 2012). In addition, the term can be used to describe the interprofessional (IP) process between professions or specialties with the goal of improving health outcomes (Gilbert et al., 2010).

Stacey el al. (2010) identified 15 SDM models from Canada, the US and UK exploring IP. Of these, 80% did not describe the methodology behind the models. Two used feedback from patients and physicians and the remaining model used grounded theory (Stacey et al., 2010). Grounded theory is applied when social interactions are explored with the aim of explaining a process; it is not used to verify an existing theory, nor is a hypotheses tested (Lingard et al., 2008). In total, the authors identified more than 150 concepts covering four main themes: Firstly, features of the process including

deliberation, knowledge exchange and acknowledgment that a decision should be made. Secondly, the individuals involved: patient and physician in addition to a decision coach. Thirdly, factors influencing the process including the macro system (eg. health system, policies) and lastly, outcomes for the patient (eg. adherence to the chosen option), outcomes for the physician and healthcare system (Stacey et al., 2010).

Legare et al. (2010) have further explored the IP relationship that defines SDM with the creation of a conceptual model. The IP-SDM Model describes the process in stages beginning with the 'Actors' (with patient at the centre) but broadened to include other players such as family members, HCPs and significant others who may be involved in the process. The process is further described leading up to the decision to be made incorporating options weighing benefits and risks, values, preferences, preferred and actual choices, implementation and outcome. The macro environment is also referenced incorporating government policies and institutional structures; the rationale being that clinical encounters cannot occur without the influence of the healthcare system in which it operates. There may be additional professionals involved in the patient's care wielding additional influence (Légaré, 2010).

Figure 3 shows one interpretation of the spheres of influence in the SDM context from classic SDM (patient-physician) to multi-focal developments and that of extended IP-SDM considerations in the wider context of decision-making described in this section and the introduction. Its purpose is to show the complexity of the SDM environment which goes far beyond the classic dyad and considers other influencers within the hospital environment but also outside of it at regional, national and international levels.

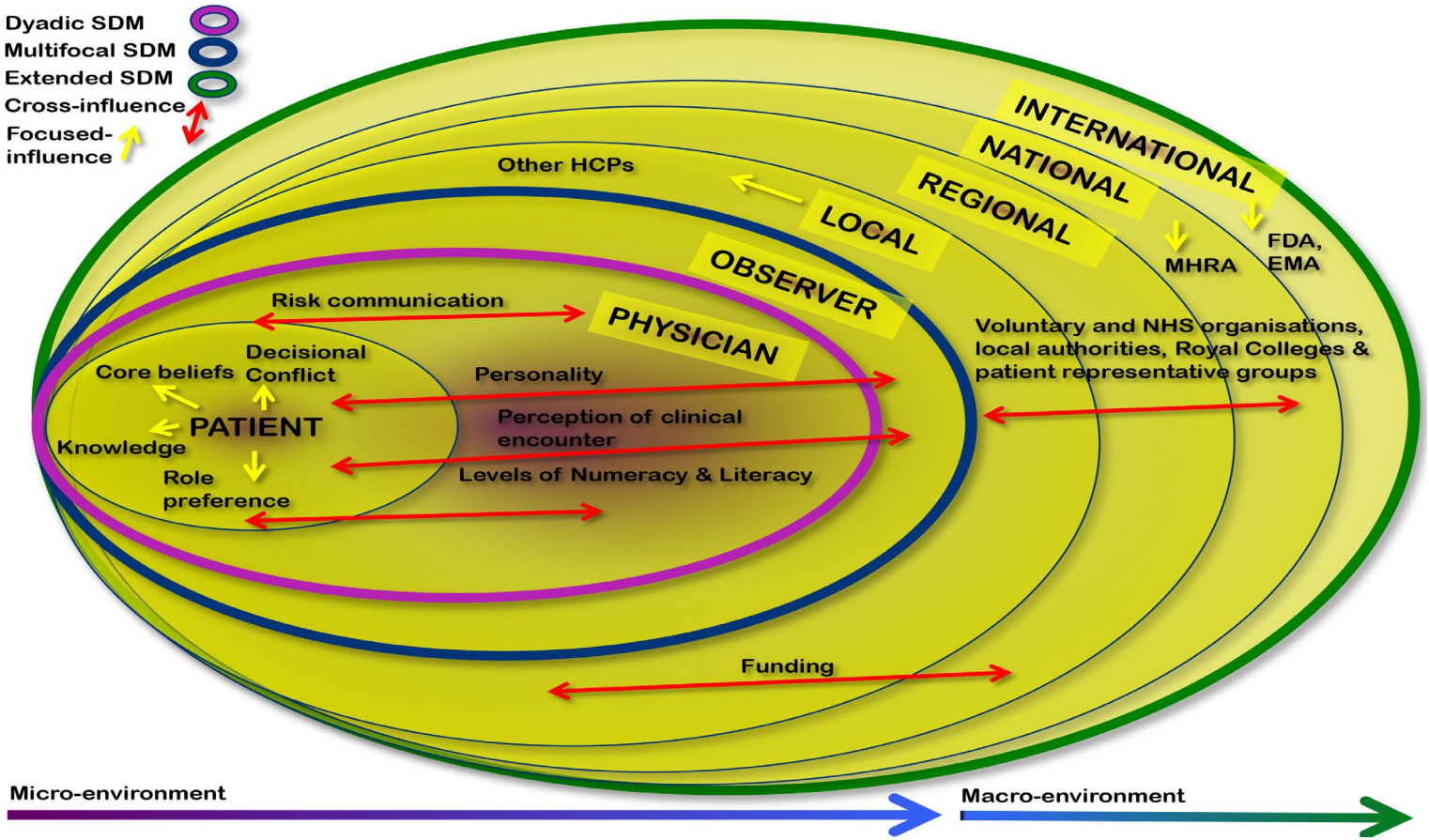

Figure 3: 'SDM: Spheres of Influence'

1.8 Measuring the decision-making process

1.8.1 Reliability & Validity

A number of measurement tools have emerged to determine the viewpoints of patients and communication skills of the doctor (see table 1). This table has been adapted and updated for completeness, combining the work of Heesen et al. (2013), Simon et al. (2007) and (Scholl et al., 2011) by Wilkie (2019). Of note, one tool appears twice in the Control Preference Scale (CPS) as its components can be used to measure pre and post-decision as to whether the original preference has been realised. Where possible, discussion of the instruments in a MS context is prioritised.

Table 1: 'List of Decisional Measurement Tools' (Heesen et al., 2013); (Simon et al., 2007) & (Scholl et al., 2011) adapted by Wilkie

MEASUREMENT	CONSTRUCT(S)	REFERENCE
PREREQUISITE		
Autonomy Preference Index (API)	Role Preference	(Hamann et al., 2007)
Control Preference Scale (CPS)*	Role Preference	(Solari et al., 2013); (Sloan J, 1997); (Ferron Parayre et al., 2013)
Decision Self Efficacy Scale	Autonomy/Self-Confidence	(O'Connor, © 1995 [updated 2010].)
KOPRA Questionnaire	Communication Preference	(Farin et al., 2011)
Krantz Health Opinion Survey	Treatment Preference	(Dinning and Crampton, 1989)
Patient Attitudes and Beliefs Scale (PABS)	Attitudes, Beliefs	(Bishop, 2010)
Preparation for Decision Making Scale	Post-DA analysis; Pre-SDM	(Bennett et al., 2010)
Scale on Participation in nursing care	Uncertainty	(Smoliner et al., 2009)
Disease Related Loss of Control	Personality	(Lohaus, 1989)
Uncertainty Tolerance Scale	Cognition	(Dalbert, 1999)**
General Self Efficacy Scale (GSE)	Personality	(Schwarzer and Jerusalem, 1995)
Items assessing information seeking	Coping Strategies/Style	(Heeson et al., 2004)
Items assessing acceptable PML risk of patients and physicians	Risk Perception	(Heesen et al., 2010)
MS Knowledge Questionnaire (MSKQ)	Disease Knowledge	(Giordano et al., 2010)
Numeracy Items for MS Patients	Numeracy	(Kasper et al., 2006)
Numeracy Items for Patients & Physicians	Numeracy/Statistic Interpretation	(Gigerenzer et al., 2007)
Perception of Prognostic Risk in MS Patients	Rick Perception/Attribution	(Janssens, 2003)

PROCESS		
Decision Support Analysis Tool (DSAT-10) (Brief version)	Quality of clinical encounter (communication, decision support)	(Stacey et al., 2008)
Decision Support Analysis Tool (DSAT)	Quality of clinical encounter (communication, decision support)	(Guimond et al., 2003)
Decision Analysis for Oncology (DAS-O)	SDM Quality in the clinical encounter	(Brown et al., 2011)
Dyadic OPTION Scale	Observing patients & physicians during consultations	(Melbourne et al., 2010)
Facilitation of Patient Involvement Scale	SDM Quality in the clinical encounter	(Martin et al., 2003)
OPTION Scale	Observing patient involvement during consultations	(Nicolai et al., 2012a); (Elwyn et al.,2003)
Perceived Involvement in Care Scale (PICS)	Patient Perception of the clinical encounter	(Lerman et al., 1990)
Rochester Participatory Decision Making Scale (RPAD)	SDM Quality in the clinical encounter	(Shields et al., 2005)
Health Care Empowerment Questionnaire (HCEQ)	Individual Empowerment	(Gagnon et al., 2006)
Planned Behaviour in MS decision making in DMTs (PBMS)	Beliefs & Values	(Kasper et al., 2012)
Protection Motivation Questionnaire	Internal Process (Motivation)	(Kopke, 2003)***
Theory of Planned Behaviour Scale (TPB-S)	Internal Process	(Godin et al., 2008)
Uncertainty in Illness Questionnaire	Uncertainty	(Mishel, 1990)
Uncertainty Profile Questionnaire	Uncertainty	(Geiger et al., 2011)
Decision Conflict Scale (DCS)	Identifying Uncertainty; Satisfaction, Decision Quality	(Legare et al, 2012)
Multifocal Approach to Sharing in SDM (MAPPIN'SDM)	Patient-Physician-Observer Interaction	(Kasper et al., 2012)
Compound Measure: SDM meeting its concepts assumptions (SDM MASS)	Patient-Physician-Observer Interaction	(Geiger and Kasper, 2012)

Observer Scale: Observing Patient Involvement (OPTION) 5 Item Scale	Patient Interaction	(Elwyn et al., 2013)
Shared Decision Making Questionnaire (SDM-Q; SDM-Q-9 item)	Patient Interaction	(Kriston et al., 2010)
OUTCOME		
Frequency of Relapses	Frequency of Relapses	(Kopke et al., 2009)
Hamburg Quality of Life Questionnaire in MS (HAQUAMS)	Health Outcome (Quality of Life)	(Gold et al., 2001)
Bereaved Family Regret Scale	Decision Regret	(Shiozaki, 2008)
Decisional Conflict Scale (DCS)	Identifying Uncertainty; Satisfaction, Decision Quality	(Légaré et al., 2012)
Dyadic Conflict Scale	Identifying Uncertainty; Satisfaction, Decision Quality	(Légaré et al., 2012)
Compound Measure: Multidimensional Measure of Informed Choice (MMIC)	Knowledge and Attitude	(Michie et al, 2002)
COMRADE Scale	Decision Outcome (Satisfaction)	(Edwards et al., 2003)
Decision Attitude Scale	Decision Outcome (Satisfaction)	(Sainfort and Booske, 2000)
Decision Evaluation Scale	Decision Outcome (Satisfaction)	(Stalmeier et al., 2005)
Decision Regret Scale	Decision Outcome (Satisfaction)	(Mancini et al., 2012)
Provider Decision Process Assessment Instrument	Decision Outcome (Provider Perspective)	(Dolan, 1999)
Satisfaction with Decision Scale	Decision Outcome (Satisfaction)	(Holmes-Rovner et al., 1996)
SURE Scale	Decisional Conflict	(Legare et al, 2010a), (Ferron Parayre et al., 2013)
* Used pre & post consultation ** Abstract-only reviewed in English *** Unable to locate online (work is a thesis)		

It is important here to distinguish between the reliability and validity of a construct. Reliability has been defined as a measurement's ability to produce results consistently when reapplied under different conditions. Validity, in this context, is evidence that conceptual measurements are realised (Field, 2009).

The underlying reliability scores of these measurements are referenced in the next sub-chapter, especially with relevance to inter-reliability where consistency across different viewpoints needs to be measured, as is the case in SDM. These include, notably, Intraclass Correlation Coefficient (ICC) and Cronbach's coefficient alpha (α).

Cronbach's α is the most widely referenced statistic when determining reliability (Vehkalahtia et al., 2006), and is used to estimate internal consistency (Peterson, 1994). It is expressed as a number between 0 and 1, sensitive to the inter-relatedness between items as part of an instrument. One of the issues with its reliability is that there is no accepted measurement score between 0 and 1. If the items of a test correlate, α value increases. That does not always guarantee a high level of internal consistency because α can also be influenced by test length. If the test length is too minimal, the α value reduces accordingly (Tavakol and Dennick, 2011).

A meta-analysis of Cronbach's α responded to a need for identifying consistency of reported α values and to determine if these matched recommendations. From a pool of >4200 α coefficients collected, the authors concluded a mean value of .77, observing 75% of reported values measuring .7 or greater (Peterson, 1994). This was consistent with recommendations put forth by Nunnally and Burnstein (1994) for acceptable

reliability levels as follows: preliminary (.70 or greater), applied research (.8 or greater) and applied research of .9 or above (Nunnally and Bernstein, 1994).

There is no consensus in the relationship between the internal structure of a test to the α value as it has been shown that a one-factor (uni-dimensional) test can have any α value. Furthermore, multi-dimensional tests can share the same α value. (Sijtsma, 2009).

Reliability has also been measured using ICC, which has been compared with α although ICC has been associated with reproducibility rather than internal consistency, as is the case with Cronbach's α (Bravo and Potvin, 1991). Other coefficients exist such as Kappa (Landis and Koch, 1977). Kappa is used for categorical data as indicated by Table 2. In contrast, ICC can be used for continuous data.

Table 2: 'Agreement Measures for Categorical Data' (Landis and Koch, 1977:p.165)

Kappa	**Strength of Agreement**
<0.00	Poor
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Almost Perfect

Table 2 shows measurement ranges utilising Kappa. Although these measurements are arbitrary in nature, applied to Kappa, they provide a useful benchmark (Landis and Koch, 1977) and could be used for other statistical measurements of this type, including ICC (King's College London, 2014).

Validity has been defined in three ways: measuring construct, predictive validity, and content validity. In the form of a measurement tool (see table 1), does it measure what it is meant to measure? In this context, the construct (eg. regret). How a construct is *validated* is dependent on prediction and content. This is further defined as being explicit about the components of the observables embodying a construct. For example, in a measure of *intelligence*, would this incorporate reason, perception *and* memory or a selection of these?. How observables are deconstructed and may interact is therefore key and studies or experiments must define which of the components of the construct married to what is expected to happen is ultimately realised and supported (Nunnally and Bernstein, 1994).

In the next section, only the most prominent measurements referenced in Table 1 are considered in detail; others are summarised. Some tools are considered elsewhere in this review most appropriate to their context eg. numeracy items, as part of a standalone sub-chapter.

1.9 Decision Prerequisites

1.9.1 Role Preference

In a review of 35 studies looking at decision interventions covering eight instruments, preferred or actual treatment choice was the most frequently occurring primary outcome measure (Kryworuchko et al., 2008).

The CPS has been cited as the most regularly used measure of patients' role preference in shared treatment decision-making and has been used effectively in an MS setting (Solari et al., 2013). The CPS comprises of five cards portraying a scenario involving treatment decision-making. Each card presents a different cartoon and statement including a preference for an active, autonomous role, sharing the decision with physician through to a passive role whereby the physician leads on the decision. The patient then orders the CPS cards by preference and the result is analysed using unfolding theory (Sivell et al., 2011). Unfolding theory maps individual choice using stimuli. This allows for individuals to be depicted by ideal points, whilst the stimuli is mapped on to a scale. The person's ideal preference corresponds to the ordering of the stimuli ranked in terms of distance (least to greatest) from their ideal point (Godin and Kok, 1996). Reliability of the CPS yielded a test-retest score, utilising Kappa coefficient, of .65 (90% agreement) (Scholl et al., 2011). To view the instrument, see Appendix C, section 5.

The KOPRA questionnaire comprises 32 items across four areas. It is aimed at people with a chronic condition and measures communication preference whilst aiming to

inform the physician or related healthcare provider. It has been shown to have good psychometric reliability (α range .80 - .92) (Farin et al., 2011).

The Autonomy Preference Index (API) comprises 23 items encompassing patient's desire for more information and role preference for participation. The tool was originally validated with an internal consistency of α = 0.8. (Ende et al., 1989). This score has been replicated in other settings including pelvic floor disorders (α = 0.8) (Flynn et al., 2006).

Hamann et al (2007) have combined API data (n=1393) from six SDM trials of chronic and acute disease, including MS. Where a higher score (0-100) represents a more active role preference, the MS group showed the highest score of 66, compared to the lowest in breast cancer (42). The authors speculate that this may reflect the nature of MS as a condition: unpredictable, the partial efficacy of treatment [at the time of writing, interferons], and the setting of the specialist out-patient setting of the trial denoting more active patients, and indicating a potential selection bias (Hamann et al., 2007).

It should be added that this study was conducted before the advent of treatments that have since emerged. It is not clear why an - albeit speculative - conclusion has been reached by the authors as to why a specialist clinic may indicate a more active patient preference. The disease comparisons are also very different in nature and course to MS: ranging from schizophrenia, depression, hypertension to oncology. HIV and rheumatoid arthritis are examples of disease comparable to MS and could be used in

this context for future comparison for reasons including: immune-related, no cure, chronic, with a range of treatments developed over a similar timeframe to MS.

1.9.1.1 Personality & Behavioural Traits

Perceived self-efficacy has been described as determining expectations and performance of a person in the context of conceived situations, and how people respond to potentially negative situations. The stronger the perceived self-efficacy, the more active the person (Bandura, 1977). The General Perceived Self-Efficacy Scale created by Schwarzer and Jerusalem (1995) is a uni-dimensional scale comprising 10 questions that users answer to what degree they agree (or disagree) with statements pertaining to scenarios. Examples include confidence in dealing efficiently with unexpected events, if they experience trouble they are able to find a solution, that they stick to aims and accomplish goals, etc. (Schwarzer and Jerusalem, 1995). Previous studies have consistently yielded Cronbach α ranging between 0.76-0.90. In a large sample of more than 19,000 patients covering different conditions from 25 countries, this appeared to be supported with an overall internal consistency measuring 0.86 and that it can be used as a universal construct (Scholz et al., 2002).

1.10 Decision Process

The OPTION scale is a measurement of patient involvement completed by independent raters assessing recordings of patient-physician consultations (audio and/or video-based). It helps determine if there are issues that need addressing, the options being considered and prioritised with the aim of eliciting a level of patient understanding and role preference evaluated as part of the SDM process. Only the

physician (or healthcare provider's) behaviour was initially assessed (Elwyn et al., 2003) although its application has since evolved to include the patient perspective (Goss et al., 2013).

In a paper published by Nicolai et al (2012) the psychometric and methodological characteristics of the OPTION scale were investigated confirming lack of support for the uni-dimensional structure purported. Reliability scores were reported as acceptable but the results were heterogeneous across studies. In particular, studies mainly failed to validate convergence. Additional issues include the lack of item independence and range restrictions, as well as failure to consider dyadic design. With this in mind, the authors note that conceptual issues and methodology need addressing so patient involvement can be measured more effectively (Nicolai et al., 2012). From this process, a revised OPTION scale has thus been developed.

Elwyn et al (2013) has proposed a shorter, revised Observer OPTION measure of SDM through identifying the core components of published models (covering 29 studies); responding to the need for greater attention to preference and integration linked to SDM. Using this framework, a revised measure was created combining data from an observational study in Canada using Observer Option 12. This has led to another, reduced version in Observer Option 5, described as being conceptually tighter, learning from the analysis of 29 studies of Observer Option 12 that have preceded it (Elwyn et al., 2013b).

As described in subchapter 1.7, it is becoming evident from SDM research, that the patient and the HCP must now be perceived as interdependent members of a dyad (or

multifocal approach when including the observer role), rather than individuals working independently (Légaré et al., 2012). Existing tools are now being adapted from their original viewpoints to incorporate this breadth, as indicated by the Multifocal Approach to Sharing in SDM (MAPPIN'SDM) developed by Kasper et al (2012). The MAPPIN'SDM model incorporates all three perspective outlined by adapting existing measurements such as the OPTION scale, DCS and others with cross-consistent content that can be applied to all parties and from which a consensus can emerge (Kasper et al, 2012).

A German RCT has tested the MAPPIN'SDM framework in clinical practice (Geiger et al., 2011) with the objective of enhancing the communication behaviour of physicians (44 in total from numerous specialties) with the use of a training intervention based on current EBPI and SDM techniques. This was achieved via a manual, training video and face-to-face feedback. The control component of the study was described as a 'waiting control group' who ultimately received the same intervention but at a later time-point. The trial was designed so that the total pool of consultations could be evaluated. Results look promising with increased SDM in the intervention group versus the control group ($p=0.05$) (Geiger et al., 2017).

The Perceived Involvement in Care Scale (PICS), is a self-reported patient questionnaire assessing their perception of the consultation. It measures three areas: the physician's facilitation and support of patient involvement, degree of information exchanged and the patient's level of participation (Lerman et al., 1990). In results taken from a German oncology study measuring pain, a modified version of the scale

(M-PICS) was used. Internal reliability of the overall scale measured by Cronbach's α has been described as good (0.87) (Smith et al., 2006); (Simon et al., 2007).

Other tools include the SDM-Q-9, a nine-item questionnaire used to evaluate the perception of patients during consultations (Kriston et al., 2010). It has since been adapted into the SDM-Q-Doc to incorporate the physician's perspective, described as the first of its type to measure this perspective using a psychometrically tested scale utilising α (0.88) (Scholl et al., 2012).

1.11 Decision Outcomes

Cited as the most popular tool of its type (Sepucha et al., 2013), the Decisional Conflict Scale (DCS) is a self-administered questionnaire comprising of 16 items developed to determine if decisional conflict is present in patients. The scale has since been adapted and tested by doctors, nurses and related healthcare providers on the basis that observed decisional conflict has helped evaluate the quality of the SDM process (Légaré et al., 2012). The conceptual framework is based on work by O'Connor (1995) and its psychometric properties aims to elicit uncertainty surrounding health-related decisions, what factors contribute to this uncertainty and perception of what might be effective in resolving the conflict. Originally the scale was evaluated in 909 individuals with a test-retest reliability coefficient using α of 0.81 (O'Connor, 1995).

From the DCS has emerged the SURE scale, a shortened version of four questions. In a randomised trial looking at the use of antibiotics for acute respiratory infections, 654 Patients reviewed both SURE and DCS post-consultation and the results were

compared for the purpose of consistency and validation. The authors concluded that the SURE scale possessed adequate psychometric properties in the primary care population with an internal consistency (using Spearman's coefficient = 0.7). A significant correlation between DCS and SURE scores was seen ($p<0.0001$) (Ferron Parayre et al., 2013). The reduced time needed to administer it is certainly advantageous but its efficacy may need further evaluation in more specialist fields outside of primary care. This could also benefit those with lower literacy skills, as has been indicated with other shortened versions of the DCS. Such variants have been used in different diseases, notably oncology (Koedoot et al., 2001).

The DCS has also been adapted for use by both the patient and the HCP as part of a dyadic approach in line with the interdependent characteristic of SDM, thus the Dyadic Decisional Conflict Scale (D-DCS) has emerged. Legare et al. (2012) have evaluated the psychometric properties of this adapted measurement combining the components of the Provider Decision Process Assessment Instrument (PDPAI) which yielded an α score of 0.90, and was an earlier adaption of the DCS aimed at HCPs. As dyadic scales should utilise the same items, unlike the PDPAI variant incorporating eight of the original DCS items, the D-DCS adapted all 16. (Légaré et al., 2012).

Decisional regret (DR) has been explored by the work of Shiozaki et al (2008) in the context of oncology and the aftermath of end-of-life decisions made by Japanese family members of those moved to palliative care units. The regret scale measurement came in the form of a questionnaire created to ask participants to rate, using a Likert scale, their level of agreement with seven statements evaluating their regret over the

decision made. Psychometric reliability of the subscales were tested using α. Results showed intrusive thoughts about regret measured 0.85 and for DR (0.79) using subscales with a retest reliability (one month later) of 70 and 69 respectively. (Shiozaki et al., 2008), (Scholl et al., 2011). The Decisional Regret Scale (DRS) containing fewer items (five in total) has since been validated in four patient populations (Brehaut et al., 2003), (O'Connor, © 1995 [updated 2010].)

One of the main outcomes arising from closer scrutiny of tools such as the DCS and OPTION scales is that agreement is emerging that some of the existing tools only consider one point of view, when in fact there is an interaction occurring between two or more parties. In order to address this, there has to be some uniformity in the content of these measures. In addition, most of the current measurements, as indicated by a review of 18 existing instruments carried out by Simon, Loh & Harter (2007), there was a majority emphasis on the patient perspective with only one measurement reflecting the physician's perspective. The tools focus on subjectivity rather than objectivity. Doubts remain over the psychometric validity of some of these tools which range from satisfactory to excellent when reported, but have not been investigated comprehensively. Functionality may differ for the same tools depending on the medical condition, as indicated by the SDM questionnaire (Simon et al., 2007).

One context in which these tools of the decisional process can be tested is through the use of a healthcare intervention where pre and post understanding can be measured as part of an RCT, as well as the consultation if relevant ('the process' as indicated by table 1). These will be considered in the next section.

1.12 Decision Support Interventions

1.12.1 Theoretical Rationale

Decisional support interventions can take many forms: Decision Aids (DA) comprising single or multi-page information guides, computer software, DVDs, CD-Roms or websites that can include official or non-official information featuring multi-media content (Stacey et al., 2011). Attempts have been made to distinguish the role of the DA from established or traditional information material, including leaflets.

As Coulter & Collins (2011) outlines, they do not tell people explicitly what to do but instead provide factual content to encourage option deliberation. They may contain a description of the condition and evidence-based facts, a list of symptoms, side-effects as well as likely prognosis with (or without) treatment; in addition, support options (Coulter & Collins, 2011: p.5).

According to its structure, which can target groups and contain a variety of components and outcome measures a DA can be referred to as a 'complex intervention' (Craig et al., 2008). To avoid confusion, it should be noted that a complex intervention can in itself take many forms of which a DA is one. It could also be applied beyond the initial definition to incorporate, as an example, a training programme (Kirkegaard et al., 2010).

In the context of this review, a DA and a complex intervention will be referred to as one. The Medical Research Council (MRC) provides a framework for the design and evaluation of complex interventions (see figure 4), acknowledging the need to process and evaluate the way an intervention under study is implemented, providing insight

into why an intervention fails or why an intervention might work and how it can be optimally supported (Craig et al., 2008), (Kasper et al., 2008).

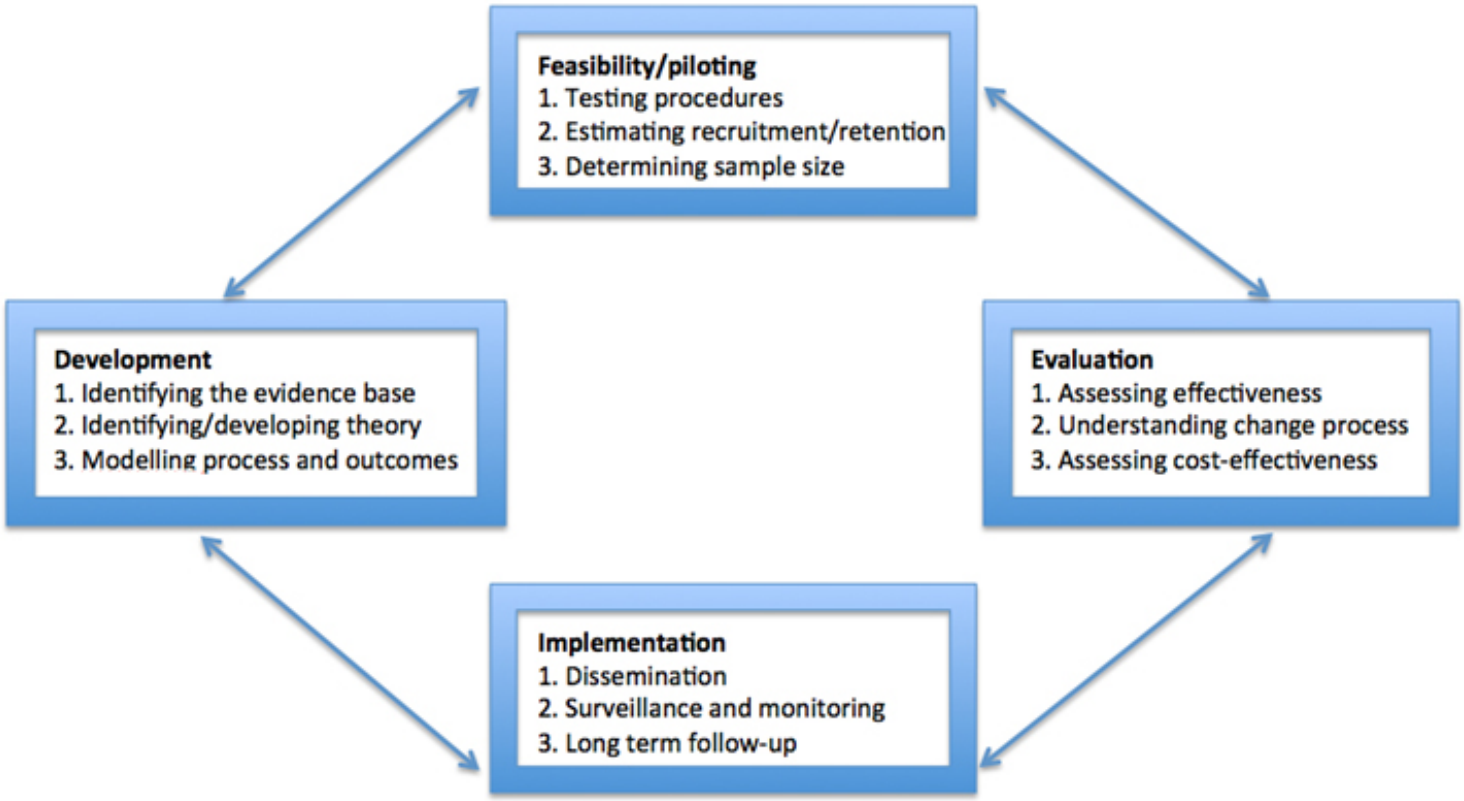

Figure 4: 'Key elements of the development and evaluation process' (Craig et. al, 2008:pg.8)

The MRC framework recommends a defined but flexible process as indicated by two way arrows in figure 4, that allows for developing the intervention systematically using the best evidence. It should be developed so it has a high expectation of a desired effect based upon similar interventions, theory, and systematic reviews and ultimately evaluated in a research setting such as an RCT. This phased approach also considers the use of mixed methodologies: qualitative and quantitative, in order to better evaluate response rates and why people choose against participating (Craig et al., 2008).

A challenge is how to best evaluate interventions: issues may arise surrounding the environment (or context) in which it is to be implemented and whether it is appropriate to its audience. Pilot studies should therefore be used initially to road-test any weaknesses in the design and test effect sizes. An African study, via this method, had originally planned to implement a classroom-based programme, but it was deemed inappropriate to cultural norms and substituted with a community-led programme in the context of evaluating it (Power et al., 2004); (Craig et al., 2008).

There is substantial evidence supporting DA efficacy but there is less information about which components are most influential for the improvement of decision *quality* (Elwyn et al., 2006). Decision quality in the context of a DA, has been defined by Sepucha et al (2013) as the quality of the decision-making *process* and that the outcome measure is met. This is further defined as the person understanding that a decision is required; that they are aware of the options and equipped to identify the priority goal married to their concerns. Furthermore, the extent to which patients' eventual choices align with their values and are implemented (Sepucha et al., 2013).

The challenge of any DA is measuring their efficacy and quality factoring the range of presentation and differing purpose. This provokes the question of on what basis the efficacy of a DA should be judged? One review concludes that, if DA researchers can agree on the primary purpose of a DA is to make a decision on a treatment option amongst multi-criteria, then DA should be examined on the basis that patients' treatment choices match their values (Kennedy, 2003).

Authors Sepucha et al (2013) have examined 86 trials of DA and the instruments used to measure the process. Criteria included an analysis of tools that measure five areas of interest (to recognise there is a decision to be made, informed about options, outcomes, goals and preferences, to discuss these with the HCP, and to be involved in the decision making process); in addition, decision *quality* comprising knowledge, managing expectation and the marriage of values to the choice made. The authors conclude that whilst evidence is strong that DA are instrumental in improving the quality of decision making (based on the constructs above), there is no standardisation. In addition, the theoretical basis for the measurement tools need further exploration. (Sepucha et al., 2013). What therefore is the theoretical evidence for guiding future interventions?

The International Patient Decision Aid Standards (IPDAS) Collaboration has been setup to guide the quality of such aids with the creation of a checklist (Elwyn et al., 2006), and was a primary outcome measure resulting from a Cochrane Review of RCTs evaluating DA efficacy for people confronted with challenging screening or treatment-related decisions.

The Cochrane review comprised a 200-year period up to 2006 (an updated review of 86 studies occurred in 2011 adding the period 2006-2009 and a further review published in 2017 included the period 2012-2015) concluding that decision aids help inform patient knowledge of their available options assisted by accurate representations of benefits and risks; to make choices aligned with their own informed values; and encourage patients to actively engage with their health practitioner as well as improve relations. The authors also noted smaller improvement when comparing detailed DA to simplified versions; but that more research is required to better understand commitment to the option chosen (if it is sustained or not and why), patient-practitioner communication, and associated costs to the healthcare system (Stacey et al., 2011).

A further update in 2014 added 33 new studies covering 34,444 participants. There was further evidence that DA improve patient knowledge and help reduce DC. The choices people make are increasingly better informed, as well as value-based. The authors note that further research is needed looking at treatment adherence, costs of implementation, and issues surrounding the content of DA such as the degree of detail targeting those with lower literacy (Stacey et al., 2014).

As a basis for the IDPAS checklist, a history of the ideal criteria required to create a patient aid has been outlined, including: the formation of a group to develop it (comprising decision experts, practitioners and patients); to clearly define the aims of the people using it; to review the DA and field test it; and to have independent reviewers assess the quality of the aid in order to identify areas that may have been

missed. This approach is based on the Cochrane review's evaluation of existing developers who have listed academic credentials and the steps taken to develop current aids. It is noted that no studies have compared the development of DA directly (Elwyn G, 2006) suggesting, perhaps, that the current checklist is merely an amalgamation of existing methods described above.

Despite a theoretical framework, DA continue to emerge without them. In addition, implementing DA into standard clinical practice has proven challenging. A Cochrane review published in 2010, evaluated the role of interventions to improve implementation of SDM by HCPs. The authors Legare et al. (2010) concluded that no definitive conclusions could be drawn from the process but that appropriate training of HCPs is key for implementing DA.

Whilst there is an ethical incitement for SDM, this must be aligned to cost and benefits of introducing interventions. It is proposed that a consensus should emerge on how SDM should be adapted into routine care to allow for cross-study comparison (Légaré et al., 2010b). Of note, the review was limited to just five RCTs, so a follow-up review may need to guide this more comprehensively once new studies have emerged.

Entwistle et al. (1998) argues that if the primary aim of a healthcare system is to improve health then DA should be sensitive to this goal (Entwistle et al., 1998). Health status can be challenging to measure argues Kennedy (2003) if the improvement in health status is small and could take years to accumulate. Another issue is that the patient may choose a treatment that fails to improve their health status (Kennedy, 2003).

In the next section, healthcare interventions and decision measuring instruments are considered as part of RCTs.

1.13 Evaluation

1.13.1 Design Implications

RCTs have been described as the 'gold standard' for testing a healthcare intervention (Akobeng, 2005), but it is important to note that bias is an issue when such an intervention is being considered as results can be influenced.

The Cochrane Collaboration provides a framework for testing bias with criteria covering random selection generation, adequate concealment of control and interventional arms, blinding of participants, study personnel and prior knowledge of outcome aims as well as incomplete data leading to selective reporting. Other bias may be evident from flawed study design (Higgins et al., 2011). The following RCTs of MS interventions will be considered in this context.

A range of methods and variations on RCTs exist for evaluating interventions including: individually randomised trials, stepped wedge designs, cluster randomised trials, and others (Craig et al., 2008). Cluster randomised trials, as the name suggests, test groups of individuals for example as part of a specialty ward, or a General Practitioner (GP) practice. This might also be used in a setting appropriate to the intervention, such as a classroom. In context, clinical guidelines could be tested whereby doctors are randomised to a group who are exposed to them and another group who aren't. The efficacy of the guidelines would be evaluated using the patients seen by both groups of doctors. Another example is in testing a vaccine which would not

have real life application if tested in individuals because the probability of an individual contracting the disease would be determined by a proportion of the population immune to the disease. Therefore, by randomising individuals, the vaccine's efficacy would be underestimated (Puffer et al., 2005).

The Stepped Wedge Design is characterised by a trial design, infrequently used, whereby an intervention is 'rolled-out' over a time period to either individuals or a cluster of people. Ultimately every participant receive the intervention but the order is predetermined. This may occur for practical or financial reasons. A systematic review of 12 studies employing the design had inconclusive results, citing lack of methodological description, randomisation methods, sample sizes and incomplete analyses (Brown and Lilford, 2006).

Trials that have tested DA in an MS context are summarised in the next section. Further information pertaining to each trial is detailed in Appendix A.

1.13.2 Clinical Application

A German study (abbreviated as ISDIMS) randomised 297 patients to one of two groups: An intervention group (IG) receiving a DA comprising a booklet about MS DMT options with an interactive worksheet and a control group (CG) receiving standard information. Neither group were informed if the information received was standard care or the new DA. The authors hypothesised that the IG would show more change in attitude within the decisional process and that this group would be less likely to make decisions with haste compared to the CG.

A Likert scale (measuring levels of agreement) was used to gain understanding of the patient's attitude towards immunotherapy at different time-points pre and post intervention. The authors hoped to see a 20% difference in role preference realised in the IG group versus the CG but no difference was seen between groups (Kasper et al., 2008). This suggests that cross-comparison of the DA's content and particularly that of the standard brochure required more scrutiny.

The 'EBSIMS' RCT covered 150 patients across three centres in Germany. The IG was exposed to a four hour educational session (with a 40 page education booklet received in advance) concerning relapse management, while the CG received an information leaflet as part of routine care. The primary outcome (endpoint) was the proportion of relapses treated with oral steroids within two years of follow-up (all patients were given the option to self-medicate using a prescription for oral steroids). The study hypothesis (a lower use of steroids in the IG compared to CG) was not confirmed. However, the IG group experienced fewer relapses than the CG group (difference = 22%; 95% CI: 11–31%). The authors suggest that this finding was as a consequence of the intervention, as patients were better able to differentiate between actual relapses and so-called 'pseudo-relapses'. The authors acknowledge that patients could not be blinded because they knew if they were in one of two programmes. Educators and assessors were also unblinded to participants' allocation, although patients were randomly assigned (Kopke et al., 2009).

A variant of a DA has been evaluated in 120 patients as part of an Italian multi-centre RCT (SIMS-Trial) evaluating the use of an information aid (IA) in the form of a

booklet and CD combined with a personal interview with neurologists (Solari et al. 2010a). This was compared to no intervention. Aimed at people within 15 days of an MS diagnosis, the rationale was to achieve a score in the highest tertile for both disease knowledge (MS Knowledge Questionnaire (MSKQ) – see table 1) and patient satisfaction with MS diagnosis communication. At one-month follow-up this composite, primary outcome was achieved in 30/60 (IG) vs. 8/60 (CG), with an odds ratio (OR) of 6.5 (95% CI 2.6-16.0). Figures at six months were 26/60 (IG) and 11/60 (CG), with OR 3.4 (95% CI 1.5-7.8). Developed in stages following MRC guidelines (see figure 4), outcome measures showed the intervention was well received.

The authors acknowledge it is not suitable in the PPMS population and there were some difficulties by the neurologists to familiarise use of the CD during the personal interview (Borreani et al., 2011); (Solari et al., 2010b). A multi-centre controlled trial assessing the effectiveness in practice in 159 newly-diagnosed MS patients has since compared the IA (updated and revised based on RCT and nested qualitative study findings) alone to the IA plus the personal interview. Results confirmed findings from the original SIMS trial but that neither method proved superior (Giordano A, 2014); (Solari et al., 2010a). The finding that the interview is not significant could prove useful for saving on clinical time (up to an hour) which would be hard to sustain in time-deficient clinics.

Building on the importance of research into complex interventions and uncertainty surrounding diagnosis, a German RCT (called PEPADIP) published results of a double-blind RCT aimed at 192 patients (aged 18-60) with early MS (CIS or RRMS).

Lasting 12 months and covering six centres, two education programmes were compared in two groups: the IG received a 57-page information booklet with recent therapeutic evidence combined with a four-hour interactive session. This was compared to a CG receiving a five page booklet and a programme focusing on stress management. The primary endpoint was informed choice (defined as a combination of good risk knowledge with harmony of attitude and uptake) being achieved at six months post-intervention. This result was seen in the IG group (59%) compared to CG (20%). Informed choice was measured using the Multi-Dimensional Measure of Informed Choice measuring risk knowledge and attitude towards DMTs. Informed Choice was further defined and said to be achieved if the patient achieved a good level of risk knowledge, positive attitude and on DMT at six months. Alternatively, informed choice could also be defined as good risk knowledge, a negative attitude and on no DMT (Köpke et al., 2014).

What can we learn from the trials that have come before? That no study has yet assessed in detail the effect of evidence-based patient information in the early MS population (Köpke et al., 2014) and, as this has been evidenced as a crucial time in which to make a decision, this is an area that merits further focus.

In addition, an on-going area of contention is what control to compare a complex intervention to in the context of an RCT in order to realistically compare (and ultimately trust) the data that results? If a control is not powerful enough and robustly tested, any intervention can look better than it is. Should existing routes of standard care, as an example, be evaluated and compared and only then be used for comparison

in an RCT of a complex intervention? Essentially this means evaluating existing methods of information communication at a local level and evaluating impact.

RCTs have been used to test healthcare interventions including DA, but as they were originally conceived for drug interventions, their design may need to be tailored further in order to minimise bias (Howard and Thornicroft, 2006). A number of variations on the RCT were thus proposed in the previous section. Current designs leave some of these studies open to bias, and in addition, as is the nature of a complex intervention, it is difficult to pinpoint appropriate outcome measures.

Coulter and Ellins (2007) have acknowledged the lack of standardisation in measuring the impact of interventions (Coulter and Ellins, 2007). This is complicated by the differing objectives of interventions and whether they are merely providing information or information with the purpose of influencing the decision - as measured in RCTs with tools that gauge impact pre and post intervention and versus a control such as standard care. In turn, these aids can be used in the context of the clinical environment as part of SDM or outside of it. Less is known about external factors such as the Internet and how medium and thus presentation may influence outcomes.

In a 2014 published Cochrane review by Kopke et al. (2014) covering 10 RCTs featuring information provision interventions with the aim of improving outcomes, results showed some evidence that disease knowledge could improve but there was less persuasive evidence that quality of life and the decision-making process could be influenced ie. improved or realised, via role preference. The authors note that there was marked heterogeneity across the studies and thus a meta-analysis could not be

executed (Kopke et al., 2014). This does suggest that a more robust framework and notably communication with researchers in the same field (as part of extended SDM – see figure 3) need to be emphasised so effective synthesis can occur.

1.13.3 Information Delivery

As this review is also concerned with information delivery in the form of mediums as well as presentation, it is important to further explore how data is represented across mediums.

Increasingly people have access - via the Internet, social media (eg. Twitter, Facebook) and other sources – to a vast range of variable quality, unregulated information with conflicting views on available therapies and information on new unproven treatments. This information may or may not be factual as in previous HCP-authored information leaflets, but is instead a mixture of facts, personal stories and viewpoints.

There is evidence that the Internet is being used for healthcare delivery (Powell et al., 2003). One question posed by authors Aitken, Altmann & Rosen (2014), was to ask if healthcare is ready for patients who are empowered and digitally demanding? It was found that younger people tend to investigate treatment options before commencing whereas the older population (50+) does so in reverse. Wikipedia has been identified as the leading provider of healthcare-related information for both patients and HCPs used at the point a treatment starts and any changes to therapy. In a survey of most viewed Wikipedia pages dedicated to types of disease over the course of a year (2013), MS was the fourth most accessed overall with 3.8 million hits compared to TB at number 1 with 4.2 million (Aitkin, 2014).

A survey looking at sources of healthcare information in >8500 US-based patients living with MS found that mass media sources, such as the Internet, was the first point of access concerning general health topics in 83% and for MS (59%) versus interpersonal information resources. However, 97% still cited the physician as the most trusted source with 40% expressing concern about the quality of the information online, although those of younger age tended to trust the internet more. Treatment was the most popular search topic (78%). Respondents were primarily female (77%) with a mean age of 56 (Marrie et al., 2013). It is not clear what type of MS the respondents had and if there are differences in approach between groups.

User statistics surrounding internet access for the purpose of healthcare information varies considerably. In 2013, 36 million adults (73%) accessed the Internet daily in Great Britain – a 20 million increase compared to 2006. Forty-three per cent searched the Internet for health-related material, utilising public health websites including NHS direct (ONS, 2013b).

Unpublished data from Wilkie and Nicholas (2012) confirmed a high level of Internet activity - both mobile and PC-based in an RRMS patient group. An anonymous questionnaire was completed by 89 UK patients' (69% female) and carers at meeting for those on natalizumab in March 2012. Of these, 29 were non-MS (parents, partners, siblings). In those with MS, 78% used the Internet once or more than once daily but 6% did not use the Internet. In those who did not use it, 45% were limited by lack of knowledge, 18% had difficulty using computers, and 18% were limited by fatigue and lack of access. In this group, 82% would use the internet more often with assistance.

In 50%, the internet played a role in their DMT decision-making process (Wilkie and Nicholas, 2012).

An immediate question that arises from this is if technology-based DA provide any advantages over traditional media, such as paper?

A systematic review performed by Sheehan and Sherman (2012) suggests that computerised DA (CDA) were comparable to non-computerised DA on various outcomes including DC and risk perception, whilst CDA were considered superior to standard education on information received indicative of the greater interactive nature of CDA including feedback modules based upon self-assessment (Sheehan and Sherman, 2012).

One study looking at a video DA aimed at patients with prostate cancer concluded that patients were more likely to take an active role in the decision-making process and that the video improved moderately memory recall in patients of treatment options and outcomes (Schapira et al., 1997). Hoffman et al (2013) looked at the internet delivery of four DA. Whilst there may be potential benefits in the form of multimedia, potential for interactivity, personalisation, customisation and accessibility, there are gaps in the research acknowledged by the authors: Firstly, clarity between DA made downloadable via the Internet, adapted to be used on the Internet and those intended for delivery on the Internet. Secondly, studies testing the use of internet-based DA in terms of user experience and quality of interaction. Thirdly, divergence of insight (psychology, health education and medicine to health informatics and ultimately a convergence of thought to guide future direction of such DA) (Hoffman et al., 2013).

1.13.4 Numeracy and Literacy

One purpose of a DA is to convey risk communication utilising evidence-based information. How this is best conveyed is dependent on how people absorb information presented differently.

There is substantial evidence that deficiencies in health literacy is aligned to poorer health outcomes and rises in health costs (Peters et al., 2007). Poor numeracy (by definition, an ability to properly understand numbers and related data, but can be extended to include probability, estimation, problem-solving and risk assessment) can lead to misinterpretation of health information and hinder communication (Peters et al., 2007); (Apter et al., 2008).

There is evidence that statistical illiteracy is prevalent amongst patients and physicians with potentially serious consequences (Gigerenzer et al., 2007). Lower health literacy has been connected to low health knowledge and reduced desire for involvement or for asking questions in the clinical setting. In a review of 97 trials, only three DA considered lower health literacy users. Health literacy was not reported in 90% of the trials (McCaffery et al., 2013).

A DA should comprise EBPI as a means of supporting an informed choice. Authors Bunge, Muhlhauser & Steckelberg (2009) have surveyed what constitutes EBPI. Analysing a combination of RCTs and systematic reviews, a number of decision interventions were considered (print-based, web and audio-visual presented) concluding that there is good evidence for graphical/numerical data whilst information-based content is derived from ethical guidelines (Bunge et al., 2010).

There is currently good evidence supporting risk perception, knowledge and understanding for numerical data and of graphics: pictographs, bar and pie charts. Based on the same criteria, evidence is lacking for pictures, drawings, patient case studies and use of different layouts and which tone of language to use (Lenz et al., 2012). Authors Hildon et al (2012) looked at 30 studies, analysing the impact of different formats of information. Where bar charts were generally preferred, tables and pictographs were easier to understand (Hildon et al., 2012).

The ISDIMS study described in the previous section, utilised a DA with content exploring pictograms of 100 human-stick figures conveying study data proportionally showing the number of people experiencing relapses and progression referencing therapeutic options (Kasper et al., 2008). A pre-study evaluated one of the modules of the resulting DA. Assessing numeracy competency using the pictogram method described, 150 participants were evaluated with an even split of 75 to a PPMS group and RRMS group. Participants were mailed the information and evaluated on their understanding of the differences between relative and absolute risk, comprehension of the information, relevance and certainty utilising CPS (information needs), visual analogue scales (emotional response) and self-efficacy scales (beliefs) (see table 1). Responses were measured before and after intervention. Results showed no adverse emotional effects from exposure to the tool and a numeracy improvement post-intervention ($P < 0.001$) (Kasper et al., 2006).

The methods behind the approach of the Kasper study described were informed by the work of Edwards et al. (2002), who have explored ways in which to turn numerical

data into understandable and meaningful pictures. Graphical displays have been used to increase the efficacy of risk communication with bar charts preferable to stick figures. Framing of information has been shown to be significant in that absolute risks should take precedence over relative risks eg. mortality versus survival data can be manipulated. Vague terms such as 'probable' and 'rare' are best avoided as people's interpretation of them can vary considerably (Edwards et al., 2002).

One example of how framing could be used in an MS context is taking natalizumab as an example. There is a marked difference between 10,000 patient years' worth of safety data collected over three years versus 5000 patient years collected over six years. Both may yield the same total patient years and be presented as the same number, but tell us very different things. This is especially relevant in natalizumab and the risk of PML because treatment *duration* is correlated with increased risk.

One solution for some could be simpler aids in the form of option grids used as part of the SDM process. An option grid summarises options and can compare them, usually restricted to six to eight frequently asked questions concerning treatment. They work best if options are limited to two or three, as this can prioritise what is most relevant and ideally in concise, simple language understandable by someone with a reading age of 10-12. One advantage is that they can be read at speed in often time-restricted clinical environments. The theoretical basis for their development is guided by NICE, IPDAS and collaboration in the form of the Option Grid Development Group (Elwyn et al., 2013a).

1.14 Additional Considerations

For people living with MS, there are considerations unique to the disease as well as part of general medicine. Some of these components have been briefly introduced but merit further consideration.

1.14.1 Cognition

Cognitive impairment affects 40-65% of people living with MS. This can manifest as memory issues, processing speed and related symptoms (Jongen et al., 2012). In a study comparing physicians' to MS patients' priorities in their healthcare, the importance of mental health rated higher than physical disability in the patient group, at odds with the opinion of the physicians (Rothwell et al., 1997)

In MS, a person's cognitive function can in turn impact on their decision-making. This may also be influenced by fatigue and depression; although efforts to understand and improve cognitive status in MS was described as still in its infancy in 2008 (Chiaravalloti and DeLuca, 2008), this is no longer the case. The area has received more focus since, including work by Langdon (2014) who has authored a website, 'Staying Smart', aimed at explaining how MS can affect memory, concentration and planning through a combination of written guides and video content (Langdon, 2014).

A person with MS may experience sensory-motor and neuropsychiatric symptoms as well as cognitive impairment (Mike et al., 2011). Cognitive behavioral therapy (CBT), exercise, and education programmes have been highlighted as promising psychosocial interventions to enable people to address cognitive issues (Jongen et al., 2012).

However, data collected by Simioni et al (2008) confirms that decision-making is preserved in early MS (Simioni et al., 2008). If treatment can have neuro-protective properties, there is again a case here for early intervention, though it must be done with sensitivity. Research by Janssens et al (2003) has shown that depression and anxiety is high in the newly diagnosed (0-24 months; primarily 0-8 months), as well as the partners of those diagnosed (Janssens et al., 2003) consistent with other research (Janssens et al., 2006), (Kern et al., 2009), (Suh et al., 2010), (Giordano et al., 2011).

As people with MS (pwMS) could be making decisions based on various levels of cognitive impairment, there may be rationale in determining participants' level of impairment in order to fine-tune existing content or tailor future content of interventions.

1.14.1.1 Neuroanatomical substrates

Neuroanatomical substrates have been associated with age-related cognitive decline but the causal relationships have proven to be more complex (Salthouse, 2011). A systemic review looking at decision-making in MS acknowledged the role of many factors including emotion and the possible role of fatigue, although the authors acknowledge the variance in group sizes and demographics across the studies, which limited how they could be compared and measured. The same study looking at 12 studies confirmed a decline in decision-making performance in the majority of pwMS (65%) compared to healthy controls (Neuhaus et al., 2018).

1.14.2 Cultural Difference

Two measurements of patient's role preference in the CPS and the autonomy preference index (API) have shown that MS patients tend to prefer more autonomous roles (versus other disease) although this does not apply to all; the research has proven sensitive to region implying a cultural origin. One study has highlighted the need for interventions that are efficacious for members of different cultural groups (Frosch and Kaplan, 1999), (Edwards and Elwyn, 2009).

Over time MS diagnosis has become more prominent in ethnic minorities including South Asians (Pakistani and Bangladeshi descent), as well as those that have moved to areas where MS is more prevalent such as Northern Europe (Elian et al., 1990) (Dean and Elian, 1997), there is logic in exploring if cultural difference is a factor as part of the decision-making process.

According to Briley, Morris and Simonson (2000) in the area of consumerism: 'cultures endow individuals with different rules or principles that provide guidance for making decisions' (p.157) (Briley et al., 2000).

It has also been suggested that there are differences between cultures in that some are more individual-orientated whilst others are more collectivist and as a consequence health care conflicts can arise (Barker, 1994) cited by (McLaughlin and Braun, 1998). Based upon this, it may be important to raise education of MS in minority groups generally (incorporating family members in the decision making process utilising tools for this purpose).

It is also worthwhile to consider realms outside of healthcare to see if the proposition is supported.

One study has looked at how the decision-making process may vary across groups in the field of further education. The Melbourne Decision Making Questionnaire, identifies coping strategies (Mann et al., 1997) of students of different cultural origin in higher education. The questionnaire was administered to samples of students in the US, Australia, New Zealand, Japan, Taiwan and Hong Kong. Students from the three Western cultures (described as individualistic) in New Zealand, Australia and US, were shown to be more confident of their decision-making abilities than students from the three East Asian, so-called group-oriented cultures (Mann, 1998).

Cultural targeting of DA that are applied generically to culturally diverse audiences is a logical step forward. A two-phase development of DA has been proposed by Alden et al. (2014) looking at cultural constructs: collectivism and individualism, with the aim of targeting patients whose cultures may vary on these attributes.

Based on theories from cognitive and psycho-social realms, one of several theories referenced is Cultural Task Theory used to understand how groups may share cultural tendencies. This is aligned with individual versus collectivist cultures, in that members of the former may be orientated towards self-promotion and taking a unique stance, whereas the latter group may seek honour or respect by following others. The authors acknowledge that the resulting intervention would need to be sensitive to degrees to which people embrace aspects of cultural orientation. DA content could be developed on this basis, emphasising role preference and further endowed with visual

characteristics, beliefs, attitudes, values and language in a healthcare context to maximize its effectiveness. Furthermore, determining the strength of cultural mindsets and how cultural norms may influence a person's approach to decision-making.

Ultimately, such a DA could be used in the SDM context reflective of the multicultural healthcare system: targeting first the cultural group and then, tailor within the culture depending on the user's choices (Alden et al., 2014). This is potentially a useful framework for further development but would need to be used with a level of caution where people do not identify with a cultural preference and could be misconstrued or offend if not implemented with sensitivity. Those with a strong and open cultural preference may however benefit from an adapted DA with tailored content.

1.14.3 Pregnancy

Pregnancy has been associated with a period of absence from MS symptoms (Lorenzi and Ford, 2002) although this has been challenged (Dwosh et al., 2003). In addition, breastfeeding post-partum has been investigated as an additional period of remission but evidence supporting this is inconclusive (Langer-Gould and Beaber, 2013), (Tsui and Lee, 2011). People on DMTs may need to consider a treatment break if there are risks associated with foetal development (Ferrero et al., 2006).

Some DMTs (interferons, glatiramer acetate) have since been tested in pregnant women versus a non-MS cohort with no major risk difference between groups (Weber-Schoendorfer and Schaefer, 2009). Those involved in clinical trials using unlicensed investigational medicinal products (IMPs), with as yet as yet unknown and on-going safety risks, may have more complicated decision-making, and may have to abandon

treatment as per trial protocol if a pregnancy arises. Men with MS must also consider the inherited risk to female partners if they are on treatment and use effective contraception in these circumstances.

An Australian-run study by Prunty et al (2008) randomly selected women with MS of child-bearing age (20-40) to one of two groups: a DA providing an overview of MS (types and prognosis) and psychosocial considerations of pregnancy: financial implications, relationship and lifestyle changes as well as case studies of people who had had children or decided against. Questionnaires were posted measuring knowledge, DC and self-efficacy. Other factors measurable in anxiety and depression were considered. The DA group (n=105) received - by post - the questionnaire with DA versus CG (N = 89) who received the questionnaire without the DA. It was hypothesised by the researchers that those receiving the DA would show increased knowledge about MS and pregnancy, certainty and self-efficacy and reduced DC; indeed the results confirmed this.

Limitations of the study, acknowledged by the authors, were the self-administrative and self-reporting aspect, with some respondents unclear about their diagnosis (type of MS, duration of disease, etc). In addition, the research setting was not controlled, the effect size was reduced due to dropout, and only 33% responded from the initial 1410 people approached (Prunty et al., 2008).

In a large study of MS patients (n=5,949) looking at the reasons behind reproductive practice in the North American MS population (both genders), the majority, almost 80%, reported no pregnancy following diagnosis. The decision was MS-related in

34.5%: reasons included symptoms interfering with parenting (71.2%), burdening partner (50.7%) and of children inheriting the risk of MS (34.7%). An additional fear cited was of the risks associated with DMTs (Alwan et al., 2013).

Despite a number of reviews confirming no detrimental effect on the course or outcome of pregnancy in the MS population (Smeltzer, 2002); (Damek and Shuster, 1997), the US study above does suggest a cautionary approach to pregnancy in some people with MS (Alwan et al., 2013).

1.15 Conclusion

Returning to the original research objectives, this literature review identified a number of findings, mainly:

There are existing drugs in MS with different efficacies and risk factors and more in development or nearing licencing. This makes decision-making increasingly complex for pwMS as well as the HCP prescribing. The emphasis on treatment is on relapsing forms of the disease although progressive MS is getting greater attention. Growing evidence suggests early treatment intervention should be considered. Decision-making is a process and attempts have been made to portion up the decision by timepoint e.g. prerequisite, process and outcome.

SDM measurements and related tools continue to evolve in order to incorporate cross-content that is measurable from the perspectives of both physician and patient (Scholl et al., 2012). The inclusion of a third-party in such settings is useful for

gaining an independent evaluation that backs-up or challenges the perception of the patient-physician as part of a multi-focal process, not solely dyadic or uni-dimensional (see chapter 4.3), (Kasper, 2012). In addition, focus on inter-professional collaboration is a growing area of research incorporating the macro-environment and other professionals who influence the decision-making process guided by the IP-SDM model.

Defining reliable and measurable outcome measures for RCTs testing DA is challenging. Due to the multi-criteria nature of decision-making, blinding of the patients, personnel, and interventional arms potentially bias results.
Role preference differs amongst MS patients and could be determined in part by culture. In addition, personality may play a role.

Numeracy and literacy levels are contributory factors as to how information is absorbed differently by individuals but are under-reported.

No study has yet assessed in detail the effect of evidence-based patient information (EBPI) in early MS and as a crucial time in which to make a decision, this requires more scrutiny.

As the CCSVI case-study highlighted, the influence over treatment decision-making is not confined to the clinical setting. As patients become more expert in managing their own care, there is a risk that outside influence, such as the Internet, can infiltrate the process - good or bad. It may also indicate a need to better interpret risk

factors pertaining to alternative therapies when fewer options exist, such as in progressive MS.

In the next chapter, the findings summarised here are investigated in three populations of pwMS. The interpretation of risk, how information is presentated, the role of the Internet and an intervention aimed at a newly diagnosed audience are explored further in Chapter 4.

Chapter 2 Comparison of MS populations – a cross-sectional study

The following chapter is part-published in the following journal: *Multiple Sclerosis Journal – Experimental, Translational and Clinical* as ' Initiating disease-modifying treatments in multiple sclerosis: Measuring the decision process using decisional conflict and decisional regret scales' https://doi.org/10.1177/2055217319833006 With permission of the co-authors (Nicholas and Solari), the information is presented as my own (as lead author) and sentences remain as published with additional content as appropriate to the chapter. The paper has been published under a Creative Commons by 4.0 licence.

2.1 Introduction

It was established in chapter one that initiating treatment is a complex decision faced by pwMS. Treatment is recommended early on in the disease course but those newly diagnosed often have minimal symptoms and other life priorities to consider, such as family planning. Those who are at a later stage of the disease may have experienced side effects or been exposed to risks that in turn impact on whether they decide to initiate treatment.

Three patient populations were therefore studied incorporating pwMS at different stages of the disease: attendees to an MS conference, an 'on treatment' cohort and an outpatient group being 'offered treatment' by neurologists. The cohorts are illustrated along a disease timeline in figure 5. The purpose of the figure is to indicate that there is a treatment window along the disease timeline which limits when a decision can be made. Within the treatment window are clinical encounters

where the prescribing of treatment can occur, but this is further complicated by regulatory restrictions (see chapter 1 – section 1.4), the interpretation of the HCP prescribing (and their own beliefs) as well as the decisional process itself from the perspective of the patient.

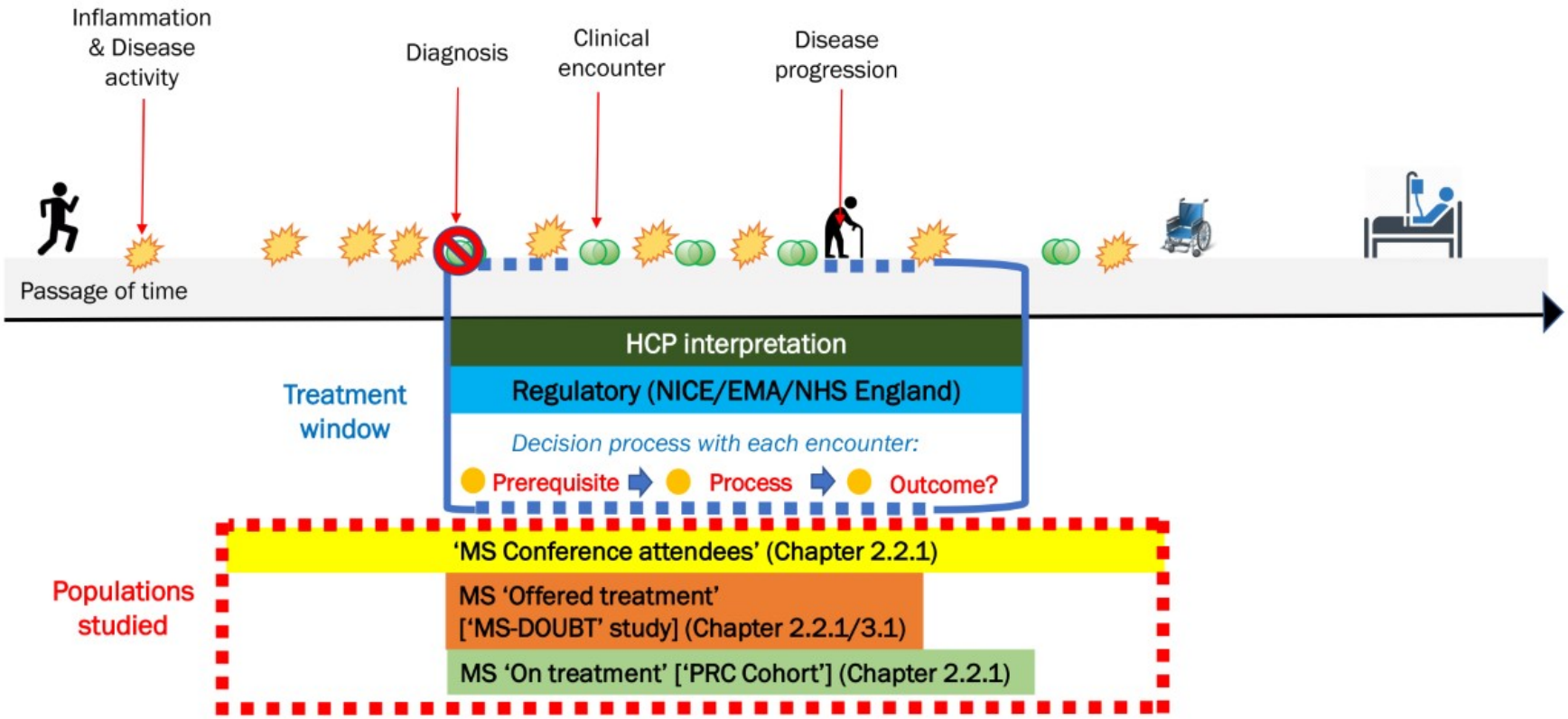

Figure 5: 'Three MS populations mapped along the disease timeline'

As described in chapter 1 and summarised in table 1, a number of decisional tools already exist, but it is unclear how the decisional process should best be measured. Therefore, a primary aim of the research was to establish if DC and DR were present in the three populations faced with a treatment decision now or previously and if DC and DR could be used as reliable outcome measures to quantify the impact on decisions in an MS population. A presence of DC would indicate if a decision, concerning treatment, was unresolved and required action. Finally the populations were compared to determine if DC and DR were present to greater or lesser degrees and to determine if other measurements were associated.

In terms of outcome measures, the SURE scale (measuring DC) was chosen because it is a validated, adapted version of the DCS (Ferron Parayre et al., 2013). Both instruments measure DC, but the SURE scale takes less time to administer. As patient time is a valuable component of a healthcare system, any instrument that could be used in a shortened form but still be used as a reliable measurement would be prioritised in this context. The Decisional Regret Scale (DRS) was used to determine if those who had previously been on treatment (or decided against it) had informed a current decision referencing treatment choice (Brehaut et al., 2003), (O'Connor, © 1995 [updated 2010].). The Decisional Conflict Gauge (DCG) is an unvalidated, visual analogue scale created by the thesis author, that asks the participant to arbitrarily mark on a scale where they feel their level of DC lies.

Finally, the CPS is an indicator of a person's preference during the consultation. This can manifest as primarily patient-led, collaborative or led by the HCP. The CPS had

been used before in an MS context (Solari et al., 2013), hence the results could be compared to other populations.

Quantifying impact was determined by quantitative multivariate analysis across the entire population with additional factors collected across cohorts. Prerequisites included MS disease type, current treatment status, ethnicity, employment status and the role preference of a person entering a consultation with a neurologist as measured by the CPS. The factors were used to determine patient priorities and ultimately if these factors drive DC and DR.

2.2 Methods

2.2.1 Participant populations

Three cohorts (n=254) participated described in order of evaluation below.

2.2.1.1 'MS Conference attendees' cohort

An 'MS conference attendees' cohort consisting of pwMS who were attending a conference in September 2014 with the aim of providing treatment strategies and healthcare advice. The invitation to the event was extended to families as well as HCPs. The event was recorded and talks can be viewed at https://www.mstccharity.org/study-day-2019.html

The 'MS conference attendees' group were approached as part of an audit thus data was recorded anonymously (Imperial College Healthcare NHS Trust neurosciences audit project). This was a standalone study and the data was only used for the purpose

of the PhD presented in this thesis. There was no entry criteria but attendees were asked to record their MS status on the paperwork.

2.2.1.2 'On Treatment' cohort

The second ('on treatment' cohort) comprised of pwMS who were part of an existing study and who were already on therapy and not seeking to change it at the time they were approached (ethics reference: 09/H0708/61). An original study aim was to provide access to new therapeutic interventions (via clinical trials), or access to second-line treatments (ClinicalTrials.gov, 2015). As the original study provided access to an existing cohort of patients 'on treatment' and there was ethical approval already in place, the chief investigator was approached about adding on the sub-study described in this thesis. The ethics were reviewed and the go-ahead given to approach the existing cohort of patients with additional questions presented here. A respondent was not selected if ≥2 years had passed since their last known clinical appointment and subjects were posted anonymised questionnaires in January 2015.

2.2.1.3 'Offered treatment' cohort

The third ('offered treatment' cohort) consisted of pwMS reviewing treatment options at outpatient clinics between April 16-April 17 as part of the Decisions Of Uncertainty Broaching Treatment in MS (MS-DOUBT) study (ethics reference: 16/LO/0153). Patients were independently selected by neurologists, they had to have RMS or SPMS, be aged ≥18 years and eligible for DMTs. The patient could be on or off-treatment at the time. This study was more expansive and will be further described in Chapter 3. This was a standalone study and the data was used for the purpose of the PhD presented in this thesis.

2.3 Questionnaires

Instruments consistent to all three cohorts were compared. The same questionnaire was used across cohorts but tweaked based upon the results of each cohort and introduced here in order of when the data was collected and analysed. See Appendix B for questionnaires.

2.3.1 MS Conference attendees cohort

The questionnaire was electronic and completed in its entirety online by attendees at the MS conference as part of the registration process. It was split into six sections:

The first section asked for demographical and disease information.

Section 2 addressed treatment knowledge and treatment status, mainly: if the respondent was currently receiving one of the treatments listed or had done so in the past. In addition, their level of knowledge across a range of treatments. The four-item SURE scale (Ferron Parayre et al., 2013), (Légaré et al., 2010a) was then incorporated as a follow-up question to determine if DC was present referencing their current treatment status.

Section 3 incorporated questions about factors influential to selecting treatment including route and frequency of administration, side effects and risk factors and pregnancy (or desire to start a family). The respondent could add additional reasons if relevant. Colleagues of the thesis author based in neurology were approached for advice on what areas to include that they felt were influential to treatment decision-making. No pre-validation work was undertaken but it was anticipated that other areas

of influence may be incorporated as the research progressed, based upon the answers provided – in particular, additional influences provided by free text commentary. Efficacy was added as a consequence of this approach.

Section 4 incorporated the five-item DRS (Brehaut et al., 2003), (O'Connor, © 1995 [updated 2010]) (again referencing current treatment status) to ascertain if DR was present referencing their treatment decision.

Section 5 listed influential parties including consultant neurologist, partner, other close relatives, friends to employer and religious (or faith) leader (as applicable).

Finally, ***section 6*** exposed the respondent to clinical scenarios using the CPS (Solari et al., 2013).

2.3.2 Treatment status

Patients were asked about their treatment status. If they were on treatment, were they happy to continue it or considering changing to an alternative treatment. Otherwise, if they were not on treatment were they still considering treatment options or not.

2.3.3 Decisional Conflict

For the SURE scale measuring DC patients were asked – 'With reference to treatment, which of the following options best reflects your current situation?'. Patients answering 'no' to one or more items (SURE total score ≤3) have clinically significant DC (Légaré et al., 2010a). See figure 6.

The SURE Tool

SURE Acronym	Items	Answer
1. Sure of myself	Do you feel sure about the best choice for you?	Yes/No
2. Understand information	Do you know the benefits and risks of each option?	Yes/No
3. Risks/benefits ratio	Are you clear about which benefits and risks matter most to you?	Yes/No
4. Encouragement	Do you have enough support and advice to make a choice?	Yes/No

Figure 6: 'The SURE Tool' ©Legare and O'Connor, 2008 cited in Ferron Parayre et al, 2013:pg.2)

2.3.4 Decisional Regret

For the DRS, patients were asked 'based upon your current treatment status (even if you are not on treatment), please show how you feel about these statements'. The statements included: 'It was the right decision; I regret the choice that was made; I would go for the same choice if I had to do it over again; The choice did me a lot of harm; The decision was a wise one. The respondent was asked to select their level of agreement with each statement from the following options: Strongly agree, Agree, Neither Agree nor Disagree, Disagree or Strongly Agree. The DRS consists of five items with a five-point Likert scale giving a score between 0 (no DR) to 100 (highest DR) (Brehaut et al., 2003). Also see section 2.6 'Statistical Analysis'.

2.3.5 Role Preference

The CPS (Solari et al., 2013) comprises of five scenarios involving treatment decision-making in a clinic setting and indicates a patient's preferred role in shared treatment decision-making. Each scenario presents a different cartoon and statement including a preference ranging from an active, autonomous role, sharing the decision with physician through to a passive role whereby the physician leads on the decision.

Here, the CPS was administered in an amended form (with permission of the lead author - Solari), whereby users were asked to pick their main preference from five patient-physician scenarios. This was because the questionnaires were not administered by the investigator and completed independently by the participant; patients were asked to pick their preferred role from the five options with reference to their most recent consultation with a neurologist. To view the instrument, see Appendix C, section 5.

2.4 On treatment cohort

The second version of the questionnaire aimed at those 'on treatment' remained consistent with the first aimed at 'MS conference attendees' aside from an additional section focusing on the patient's most recent clinical encounter. The inclusion of this additional measurement was informed by an article published in the British Medical Journal (BMJ) by Roberts et al (2014), detailing the results of a questionnaire measuring primary care across the UK. Patients were asked to rate the quality of their GP surgery: a measurement of the HCPs as well as the surgery-related services. Within this questionnaire was a section asking the patient about communication within the clinical encounter. Scores were then compared across primary care (Roberts et al., 2014). As consultant neurologist came out as the most prominent individual in treatment decision-making, and the growing trend towards SDM, it was decided that this section could be lifted and incorporated into a second questionnaire, adapted from the first cohort.

In addition, as the first cohort of patients were actively seeking out information as

part of an MS conference, it was necessary to see if other MS patients shared the same opinion on treatment decision-making or differed. For comparison, the 'MS conference attendees' questionnaire was used and adapted a second time in 2014, and posted to participants in January 2015 for completion as part of the on-going Patient Research Cohort – Rapidly Evolving Multiple Sclerosis (PRC-REMS) (ClinicalTrials.gov, 2015). PRC-REMS in this context is the same as the 'on treatment' cohort referred to henceforth.

The referenced encounter was defined as the patient's most recent neurology outpatient appointment and identified using the hospital's patient tracking system. A respondent was not selected if $\geq$2 years had elapsed since their last known clinical appointment, as it was considered too long ago for reasonable consideration and recall by the patient. Patients (n=156) were thus identified and a paper copy of the questionnaire was posted with an option to complete the same questionnaire electronically at http://www.surveymonkey.com/s/msrems. This link was referenced in a cover letter (with a password to prevent other user access) addressed to the patient, including the date of their most recent neurology encounter and who it was with. If the clinic visit was different to the recorded date, the patient was asked to enter this additional information manually. All responses were anonymised and a 50% response rate was achieved.

The primary goal of the research cohort (n = 200) and which had previously received favourable ethical review (ethics reference: 09/H0708/61) was to provide patient access to clinical trials testing new therapeutic interventions or access to second-line

treatments (ClinicalTrials.gov, 2015). The patients were therefore contacted for their opinion.

2.5 Offered treatment cohort

The questionnaire aimed at the 'offered treatment' cohort remained consistent with that completed by the 'on treatment' cohort. Based on the findings of the previous two cohorts, the parties of influence section was increased to incorporate physiotherapist, occupational therapist and MS nurse. The subsequent inclusion of the MS nurse was a belated omission that should have been included in the original questionnaire, reflective of the growing importance of this role. Around 300 MS nurses are currently practicing in the UK but 80% of MS patients have reported that there are not enough nurses to provide the support needed (MS_Trust, 2018b). The opportunity was provided to free text an answer of any other parties of influence that the respondent felt influenced their treatment decision-making. Additional measures were introduced which were unique to this cohort and this data will be reviewed in Chapter 3.

However, for the purpose of comparison, only the data which was consistent across all three cohorts are being presented in this chapter. The exception is parties and factors of influence determining treatment choice, which was consistent across cohorts but added to as the study progressed and in response to feedback. Therefore additional data is presented for the later cohorts only.

2.6 Statistical analysis

MS type was categorised as relapsing remitting (RR)MS, SP/PPMS; MS duration: 0-3 years, ≥4 years; sex; age group 18-44, 45 and above; ethnicity: white (all) or other (all) incorporating black, asian, mixed & all other groups (due to smaller numbers it was not possible to stratify the ethnic groups further); marital status: with partner (married, co-habiting, civil partnership, single (separated, divorced, single); employment status: employed: full/part-time, self-employed or other state of employment, or not in employment: disabled, retired, homemaker, unemployed, student or other.

Subjects were asked to choose one of four options to categorise them into two groups by treatment status: 'satisfied': on or off treatment but satisfied with current status or 'not satisfied': on or off treatment and considering options; Treatment naïve patients or with treatment history;

Cohorts were coded as 'MS conference attendees', 'on treatment', 'offered treatment'.

CPS was classified as Active, Active-Collaborative, Collaborative, Passive-Collaborative, Passive.

SURE groups were classified as DC: yes or no.

Parties and factors of influence were grouped by 'influential (incorporating fairly and highly)', no influence.

Treatment potency was classified as no treatment, moderate or high potency – as defined by the Association of British Neurologists criteria (Scolding et al., 2015). The main reason for using professional facing guidelines was to distinguish treatment potency across the spectrum of treatments now available in MS. It was therefore most appropriate to consult clinically qualified consensus among neurologists in the specialty of MS.

Items 2 and 4 of the DRS were reverse coded as per the creator's instructions. A higher number indicative of more regret. Scores were converted to a 0-100 scale by subtracting 1 from each item then multiplying by 25. To generate a final score, the items were summed and averaged. A score of 0 represents no regret; a score of 100 represents high regret (Brehaut et al., 2003).

Data is presented as ratios, percentages and mean and standard deviation where appropriate. Statistical analysis was performed using the paired T-test, two-way ANOVA (GraphPad Prism, version 7.02 September 2016: www.graphpad.com). Categorical frequency data was analysed using χ^2 and Fishers exact test (Vassarstats: www.vassarstats.net accessed 04/02/2018) where appropriate. Modelling the dependence of the three scores (DC, DRS and CPS) on the covariates was performed using logistic regression models using R (version 3.4.2: 28-09-2017). Covariates were described as odds ratios, reported with 95% confidence intervals and p values testing

the null hypothesis of no effect. Graphs were drawn using (GraphPad Prism, version 7.02 September 2016: www.graphpad.com).

2.7 Results

2.7.1 Population characteristics

105/116 responses obtained from the 'MS conference attendees' cohort were complete. One hundred and sixty-nine pwMS were sent questionnaires in the 'on treatment' cohort, 78 responded (46% response rate) of which two responses were incomplete. One hundred and twenty-nine pwMS were approached as part of the 'offered treatment' cohort, 73 responded (57% response rate). Two hundred and fifty-four pwMS were part of the total analysis (73% female, 92% RRMS); their demographics are described in Table 3. Treatment naïve subjects were derived from the 'MS conference attendees' and 'offered treatment' cohorts.

2.7.2 Medium access to questionnaires

The 'MS conference attendees' cohort could only access questionnaires electronically. This comprised of tablet (29%), PC (26%) laptop (26%), smart phone (19%), 5 missing. The 'on treatment' cohort could complete questionnaires electronically or by paper. Sixty-nine per cent of respondents completed the questionnaires by paper method, PC (13%), laptop (9%), smart phone (1%), and by tablet (8%). The 'offered treatment' cohort could only complete the paperwork by paper method.

Table 3: Demographic features of the three cohorts of pwMS.

Parameter	Frequency, %, missing												
	Combined cohort (n=254)			**'MS conference attendees' (n=105)**			**'On treatment' (n=76)**			**'Offered treatment' (n=73)**			**P-value (comparing cohorts)**
Relapsing MS*	229, 92%, 5			87, 85%, 2			74, 100%, 2			68, 94%, 1			p=0.0006
MS diagnosis (0-3yrs)**	64, 26%, 12			32, 30%, 3			0, 0%, 5			32, 46%, 4			p<0.0001
Treatment naïve***	36, 14%, 3			14, 13%			0, 0%			22, 31%, 3			p=0.003
Treatment potency (no treatment (0), moderate (1), high (2))**** number on [injectable/orals]	0=67, 28 %	1=96,39 % [35, 60]	2 = 91, 33 %	0=17, 16 %	1=28, 27 % [17, 11]	2 = 60, 57 %	0=11, 15 %	1=38, 50 % [11, 27]	2 = 27, 35 %	0 = 39, 53 %	1=30, 41 % [7, 22]	2 = 4, 6 %	p=0.000
Male sex	68, 27%			31, 30%			20, 26%			17, 23%			NS
Age 18-44 years	136, 54%			48, 46%			48, 63%			40, 55%			NS
White ethnicity	206, 81%, 2			89, 85%			58, 77%, 1			59, 82%, 1			NS
With partner	159, 65%, 10			76, 72%			50, 66%			33, 52%, 10			NS
Employed	149, 61%, 8			56, 53%			48, 64%, 1			45, 68%, 7			NS

*Differences in the ratios of MS type (PPMS/SPMS & RMS) between the groups (p=0.0006) was due to SPMS/PPMS participants being excluded from the 'on treatment' and 'offered treatment' cohorts as a result of their study entry criteria.

**There was a higher proportion of newly diagnosed (0-3 yrs) pwMS in the 'offered treatment' than the 'MS conference attendees' cohort (p=0.046) and the 'MS conference attendees' cohort had a higher proportion of newly diagnosed pwMS than the 'on treatment' cohort (p=<0.0001).

***There were in total 36 (14%) treatment naïve pwMS, none in the 'on treatment' cohort, significantly less than the 'MS conference attendees' cohort (14/105 [13%], p=0.0009), and the 'offered treatment' cohort (22/70 [31%], p=<0.0001). There were significantly more treatment naïve pwMS in the 'considering treatment' versus the 'MS conference attendees' cohort (p=0.003).

****The moderate and high potency treatment groups were compared and found a significant difference (2x3 Fisher's Exact Test, p=0.000) confirming that the 'MS conference attendees' cohort had a higher percentage on high potency treatment. This cohort also had the lowest percentage of treatment naïve pwMS.

NS – not significant

Treatment naïve pwMS and those 'offered treatment' have high levels of dissatisfaction with their current treatment status

The treatment status 'not satisfied' was found in 44% (113/254) of the total population; 33% (35/105) of the 'MS conference attendees' cohort, 25% (19/76) of the 'on treatment' cohort and 81% (59/73) of the 'offered treatment' cohort. This was significantly higher in the latter (chi square, $p<0.0001$) consistent with a decision needing to be made. Treatment status 'not satisfied' was also high in those who were treatment naïve where 26/36 (72%) were 'not satisfied' with their current treatment or lack of treatment. Notably a majority were in the 'offered treatment' cohort and a multivariate analysis of the total population using the initial factors: age, gender, ethnicity, employment status, marital status, type of MS, time from diagnosis, treatment naïve and cohort found that only being from the 'offered treatment' cohort (1.608 [1.408, 1.836], $p<0.0001$ (odds ratio [95%CI: lower, upper], p)) was associated with being 'not satisfied' with treatment status (adjusted R^2 0.214, $n=254$, $p<0.0001$).

Treatment naïve pwMS have high levels of DC and DR whereas those 'on treatment' have low levels of DR

In the total population 53% (135/254) of pwMS were found to have DC. This was significantly increased to 27/36 (75%, $p=0.013$) in the treatment naïve group. Fifty-nine per cent (62/105) of the 'MS conference attendees' cohort had DC, 53% (39/73) in the 'offered treatment' cohort and 45% (34/76) of the 'on treatment' cohort. There were no significant differences between the cohorts. There was a peak of high DR in the treatment naïve group compared to those who were or had been on treatment

(Figure 7). There was a difference between the cohorts in terms of their DRS score (Figure 8, Krushal-Wallis, p=0.0005) with the 'on treatment' cohort having significantly less DR than the 'MS conference attendees' (p=0.0028) and 'offered treatment' cohort (p=0.0016).

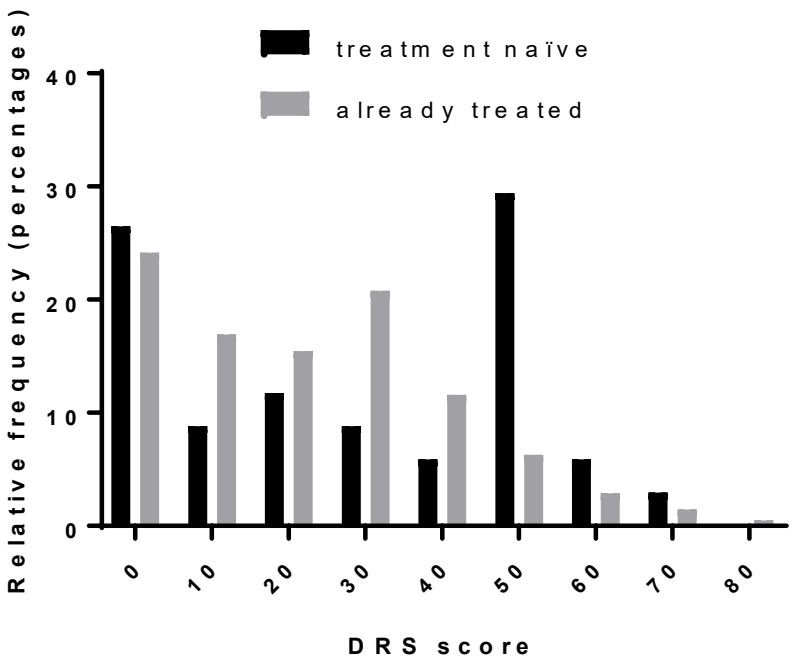

Figure 7: 'The DRS scores patients who are treatment naïve versus those who were on of who had been on treatment' (Wilkie et al., 2019).

There is a significant difference between the distributions of DRS scores in the treatment naïve cohort (n=36, 3 questionnaires not completed) versus those who were or who had been on treatment (n=215, 3 questionnaires not completed) (Kolomogorov-Smirnov test, p=0.027).

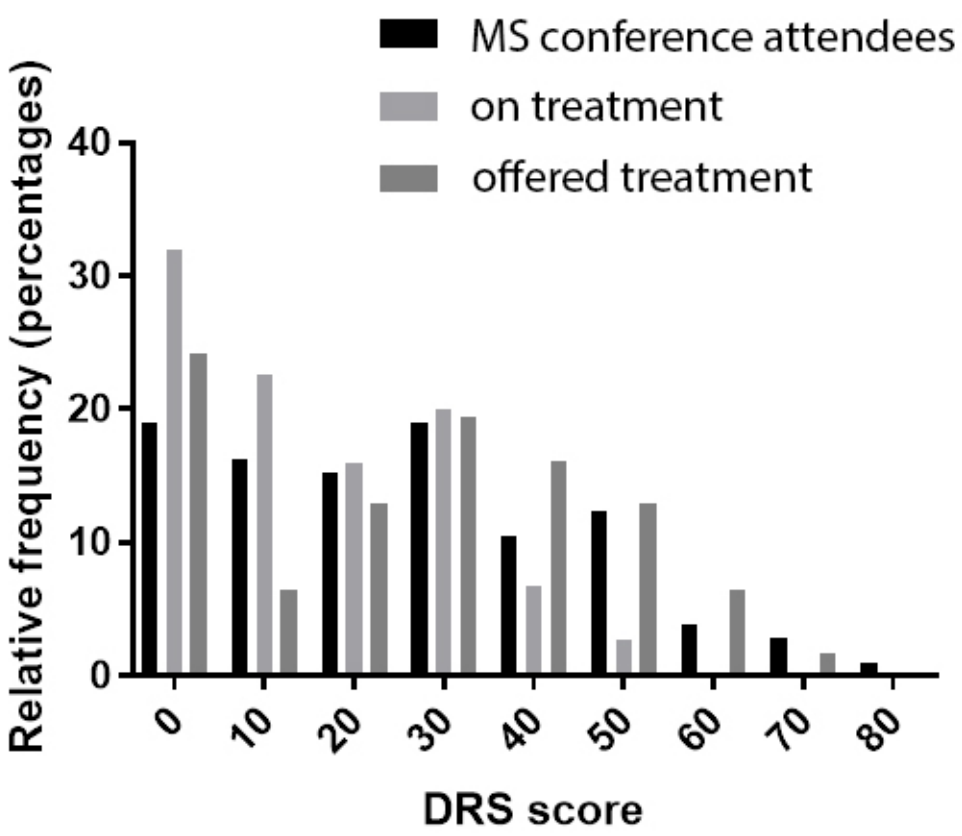

Figure 8: 'Comparison of cohorts by DRS' (Wilkie et al., 2019)

The 'MS conference attendees' cohort had the highest DR compared to the 'on treatment' cohort. Notably the 'offered treatment' cohort had a lower DRS score as many had not been on treatment.

Highest levels of DC in pwMS 'not satisfied' with current status are seen in 'offered treatment' cohort

Thirty per cent (77/254) had both DC and dissatisfaction with their treatment status; 30% (31/105) of the 'MS conference attendees' cohort, 18% (14/76) of the 'on treatment' cohort and 44% (32/73) of the 'offered treatment' cohort. The 'offered treatment' group 'not satisfied' with their treatment, had significantly higher DC compared to those 'on treatment' (p=0.000) and the 'MS conference attendees' cohort (p=0.049), whereas there was a trend for a difference between the 'MS conference attendees' and 'on treatment' groups (p=0.088). In the total treatment naïve population, 72% (26/36) were not satisfied and recorded DC. Confirming that DC is affected by other factors 58/135 (43%) had DC but were satisfied with their treatment status.

Treatment satisfaction and DC and DR are only associated in those who are on treatment not in those who are treatment naïve

Treatment satisfaction and DC and/or DR were associated in those who had not yet started treatment e.g. treatment naïve and in those who were on treatment. As expected in those who were treatment naïve, treatment satisfaction was not associated with DC or DR (n=34, adjusted R^2 -0.015, p=0.48). However, in those who were on treatment, treatment status was associated independently (n=210, adjusted R^2 0.165, p=0.000) with both DC (1.161 [1.020, 1.322], 0.024) and DR (1.009 [1.006, 1.013], 0.000).

DC and DR in the total population are increased by dissatisfaction with treatment, lower potency treatment, being employed and having more reliance on the doctor's decision

To gain further insight into factors that may influence DC and DR, a multivariate analysis was performed with the following co-variates: age, sex, ethnicity, employment, marital status, MS disease type, time from diagnosis, treatment status, cohort and treatment potency. Five variables were associated with DC (n=245, adjusted R^2 0.142, p=0.000; Table 4, column 1) and four variables were associated with a higher DRS score (n=241, adjusted R^2 0.222, p=0.000; Table 4, column 3).

Having DC and DR were both associated with being from the 'MS conference attendees' cohort, being on a lower potency treatment, dissatisfaction with treatment and being of non-white ethnicity. In addition, DC was associated with being employed. Though there was a correlation between disease duration and employment status in the total cohort (47/63 employed and disease duration of >4 years vs 96/173 (75%) employed and disease duration 0-3 yrs; χ^2 p=0.010); disease duration itself was not associated with DC.

A similar multivariate analysis was performed for the CPS, using the same initial variables as for DC and DR. In contrast, more passivity was associated with non-white ethnicity and having RRMS disease type (n=233, adjusted R^2 0.064, p=0.000; Table 4, column 5). The role of ethnicity is illustrated in Figure 9, where being of non-white ethnicity is associated with more passivity (Kolomogorov-Smirnov test, p=0.006). When CPS was added to the models predicting DC (n=236, adjusted R^2

0.137, p=0.000; Table 4; column 2) and DRS (n=235, adjusted R^2 0.232 p=0.000; Table 4; column 4), CPS was a significant factor for both DC and DRS and in both cases ethnicity became non-significant. This implied that higher CPS e.g. more reliance on the doctors' decision rather than ethnicity, was associated with more DC and DR.

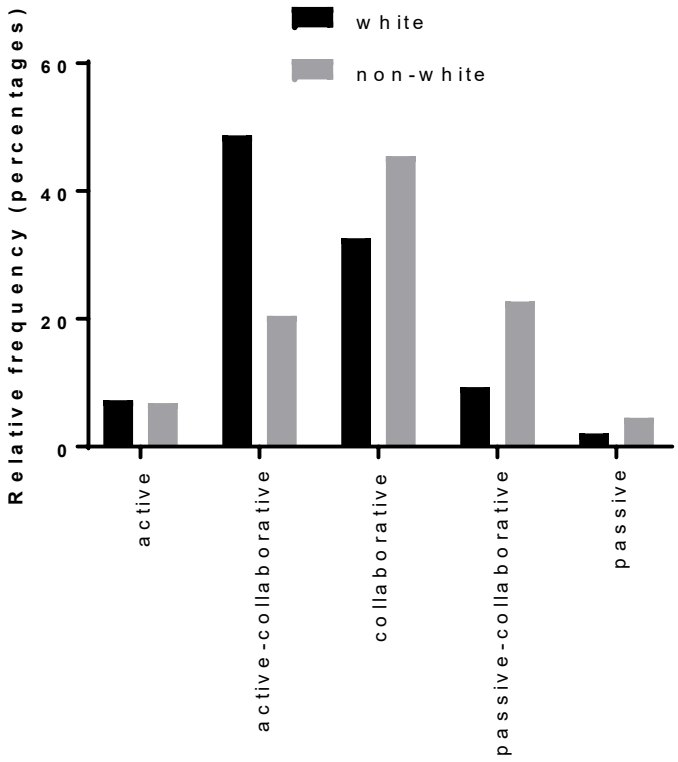

Figure 9: 'Distribution (% of total) for each category of the CPS score from the total population' (Wilkie et al., 2019)

Non-white ethnicity scored significantly higher CPS scores (representing a passive role) compared to white ethnicity (Kolomogorov-Smirnov test, p=0.006).

Table 4: Multivariate analysis of factors associated with DC, DRS and CPS with the factors: ethnicity, employment, treatment status, cohort, MS type and treatment potency.

DC (column 1) was associated with less satisfaction with treatment, being part of the 'MS conference attendees' cohort, being of non-white ethnicity, being in employment and on a less potent treatment. High levels of DR (column 3) was associated with being less satisfied with treatment, being part of the 'MS conference attendees' cohort, being of non-white ethnicity and being on a less potent treatment. Higher CPS (column 5) e.g. more passivity in decision-making, was associated with non-white ethnicity and RRMS phenotype. When CPS replaced ethnicity as a variable it was then significant in the model (DC - column 2; DRS - column 4).

Factor	**Odds ratio (95%CI upper, lower), p**				
	DC	**DC with CPS instead of ethnicity**	**DRS**	**DRS with CPS instead of ethnicity**	**CPS**
Treatment status	1.253 (1.087, 1.444), 0.002	1.224 (1.077, 1.437), 0.003	48728 (321.1, $7.7.39x10^{6}$), 0. 000	65248 (417.1, $1.02x10^{7}$), 0.000	-
Cohort **Reference is c1 unknown Rx**	Cohort 2. 0.841 (0.730, 0.970), 0.017 Cohort 3. 0.724 (0.613, 0.855), 0.000	Cohort 2. 0.845 (0.729, 0.979), 0.025 Cohort 3. 0.724 (0.612, 0.857), 0.000	Cohort 2. $1.6x10^{-5}$ ($1.1x10^{-7}$, 0.002), 0.000 Cohort 3. 0.0005 ($1.2x10^{-6}$, 0.172), 0.011	Cohort 2. $1.9x10^{-5}$ ($1.1x10^{-7}$, 0.003), 0.000 Cohort 3. $3.9x10^{-4}$, (1.0x10-6, 0.148), 0.010	-
Employment	1.173 (1.039, 1.323), 0.010	1.186 (1.047, 1.343), 0.007	-	-	-
MS disease type	-	-	-	-	0.612 (0.412, 0.909), 0.015
Treatment Potency	0.875 (0.800, 0.958), 0.004	0.872 (0.796, 0.956), 0.004	0.006 (0.0002, 0.157), 0.002	0.007 (0.0003, 0.163), 0.002	-
Ethnicity	1.192 (1.023, 1.389), 0.024	NA	860.093 (3.83 7, $1.9x10^{5}$), 0.015	NA	1.616 (1.210, 2.156), 0.001

CPS	NA	1.093 (1.022, 1.170), 0.010	NA	77.67 (7.089, 851), 0.0004	NA

Consultant neurologist is the most important influencer in all with differences seen between cohorts referencing partners, friends and family

The consultant neurologist was identified as the most significant party involved in treatment decision-making in 96% of the total population. The MS nurse was also seen as highly influential in the 'offered treatment' cohort (92%). See table 5.

Significant differences were observed when the cohorts were compared. Fifty-five of 76 (72%) of the 'on treatment' cohort valued partner as influential compared to 63/105 (60%) of the 'MS conference attendees' cohort and 35/64 (55%) in the 'offered treatment' group (p=0.000). The 'offered treatment' cohort placed more emphasis on other close relatives (p=0.003) and friends (p=0.007) versus the other two cohorts.

Relevant to the 'offered treatment' cohort only, six commented on additional parties of influence that they considered significant. These included: other patient experiences/MS websites including Facebook groups and the opinion of children. One user commented that they spend "a lot of time in hospitals for various check-ups. I am not sure Tysabri [as a monthly infusion] would be popular with home schooling. Bored kids in hospital would be a consideration". Another said that treatment involving blood products would be a deciding factor referencing their faith but differentiated this from 'faith leader' as being non-significant.

Efficacy is the main factor influencing treatment decision-making

Efficacy was the most influential factor followed by consideration of side effects when initiating treatment. There were no significant differences observed when the cohorts were compared. See table 5.

The clinical encounter

The main themes of the consultation that the patient classed as relevant were consideration of 'Involving you in decisions about your care' (B, lower, upper CI, p-value: .151, .019-.282, .025) and 'taking your problems seriously' (.162, .038, .286, 011) (n=71 Adjusted R^2 .331, p=0.000).

Table 5: Parties and factors involved in treatment decision-making: levels of influence

Parameter: Parties Influential	Frequency, %, Missing				
	Combined cohort (n=256)	**'MS conference attendees' (n=105)**	**'On treatment' *(n=78)**	**'Offered treatment' (n=73)**	**P-value (comparing cohorts)****
GP	54, 22.1%, 12	23, 21.9%	16, 21.3%, 3	15, 23.4%, 9	NS
Cons Neurologist	238, 96.3%, 9	100, 95.2%	78, 100%	60, 93.7%, 9	NS
Partner	153, 62.4%, 11	63, 60.0%	55, 72.3%, 2	35, 54.6%, 9	p=0.000
Other close relatives	102, 41.6%, 11	33, 31.4%	32, 42.1%, 2	37, 57.8%, 9	p=0.003
Friends	54, 22.0%, 11	18, 17.1%	13, 17.1%, 2	23, 35.9%, 9	p=0.007
Employer	18, 7.3%, 10	7, 6.7%	6, 7.7%, 1	5, 7.8%, 9	NS
Faith leader	9, 3.6%, 10	6, 5.7%	0, 0.0%, 1	3, 4.7%, 9	NS
***Physiotherapist**	-	-	-	7, 10.9%, 9	-
***Occupational Therapist**	-	-	-	6, 9.3%, 9	-
***MS Nurse**	-	-	-	59, 92.1%, 9	-
Parameter: Treatment factors Influential	**Combined cohort (n=256)**	**'MS conference attendees' (n=105)**	**'On treatment' (n=78)**	**'Offered treatment' (n=73)**	**P-value (comparing cohorts)**
Route of Admin	185, 76.1%, 13	78, 75.0%, 1	60, 80%, 3	47, 73.4%, 9	NS
Frequency	177, 71.9%, 10	75, 71.4%	56, 72.7%, 1	46, 71.8%, 9	NS
Side Effects	220, 89.7%, 11	94, 89.5%	67, 88.2%, 2	59, 92.1%, 9	NS
Risk Factors	212, 87.2%, 13	90, 85.7%	66, 88.0%, 3	56, 88.8%, 10	NS
Pregnancy	53, 21.8%, 13	17, 16.2%	19, 25.7%, 4	17, 26.5%, 9	NS
****Efficacy**	-	-	73, 100%, 5	62, 96.8%, 9	NS

* Up to 78 respondents responded to this section of the questionnaire

**2x3 Fisher's Exact two-tailed χ^2 test used with the exception of 'Efficacy' (2x2 table used).

***Applies to 'Offered treatment' cohort only

****Applies to 'On treatment' and 'Offered treatment' cohorts only

NS=Non-significant

2.8 Discussion

Three populations of pwMS were included in a cross-sectional study to try and determine the role of treatment in decision-making about DMTs in MS. The combined populations showed a high level of dissatisfaction (44%) with their treatment status (on or off treatment) with highest levels in the treatment naïve subgroup. On a cohort basis, this was highest in those 'offered treatment' and lowest in those 'on treatment'. This is not surprising as the 'offered treatment' cohort had just come from a consultation where it was made clear there were decisions to be made whereas the 'on treatment' cohort did not make active contact to discuss therapy.

The majority of the total population had DC (53%). However, in contrast to dissatisfaction with treatment, DC was highest in those from the 'MS conference attendees' cohort - significantly above the 'on treatment' population. This was increased further when those in each cohort who were not satisfied with their current treatment status were studied.

The high levels seen in the 'MS conference attendees' cohort is interesting in that this group were attending a conference aiming to inform about MS therapies. That they were part of an anonymous audit and were not part of a study, highlights a potential issue in understanding the aetiology of DC. Firstly, their attendance at a conference (with DC present) indicates actively seeking knowledge possibly to resolve DC - however it was not possible to contact them directly to confirm this.

Secondly, in-depth studies may be biased as a result of not engaging sections of the MS population. Again, the low levels of DC found in the population contacted at home who have not sought out nor attended clinic - where issues of treatment would have been raised - is not surprising. Reassuringly, the findings using the DRS scale, essentially reflect the DC findings, further validating the results.

DC and DR have been related here to the process of starting treatment in MS to determine if and how they change when started. This was achieved by relating to specific questions about a patient's current status with regard to treatments: either satisfied with what they are on or that they are not on treatment in the case of those who are treatment naïve. DC and DR are influenced by multiple factors and indeed there is high DC and DR in treatment naive patients, but it is not correlated to treatment satisfaction where DC and DR is correlated with treatment satisfaction in those on treatment.

The quantitative multivariate analysis performed across the total population highlighted other factors associated with DC and DR; this included; being on lower potency treatment that was still evident when the treatment naïve group were removed, more passive involvement in decision making, whilst being in employment was associated with higher DC alone.

The association with lower DC and DR in those on treatment and higher potency treatment reinforces the finding that treatment is associated with reduced DC. It may relate to stronger treatments having greater beneficial impact on quality of life (QoL)

(Rice et al., 1999) or it could also relate to reduced day-to-day side-effects associated with high potency therapies (Coles, 2015). It is a vital issue for HCPs to be aware of as there may be a desire amongst pwMS to access higher potency treatments to achieve the best possible outcomes.

Non-white ethnicity was initially identified as a potential factor influencing DC and DR. As has been seen previously in multiple populations, it was found that a more passive role preference was related to ethnicity (Giordano et al., 2008), (Ratanawongsa et al., 2010), (Heesen et al., 2004). Consistent with this, when CPS was added to the factors associated with DC and DR, ethnicity became non-significant, implying a more passive role preference was associated with more DC and DR.

Increased patient involvement and SDM has decreased DC in other conditions and in turn lower DC had a favourable influence of patient satisfaction with the HCP (Hölzel et al., 2013), (Kremer et al., 2007). This supports involvement of the patient during the clinical encounter but whether this is realised depends on the perception of the patient. Unexpectedly, it was also found that being in employment was associated with DC. Some studies have associated unemployment with a prolonged disease duration (Lunde et al., 2014) but here disease duration was not found to be independently associated with DC and DR. The association may occur through a confounder not measured - such as fatigue (Smith and Arnett, 2005).

This study has a number of limitations. Decision-making is a process and many factors influence DC and DR; as a result it is necessarily imperfect concentrating the measured DC and DRS on a decision to start treatments. Furthermore, DC is not a binary response as measured here and the many facets of DC were not captured here. Finally, this study is cross-sectional thus differences seen in those who are treatment naïve and on treatment need to be replicated longitudinally.

Earlier work implied that DC was not involved in the decision-making process (Köpke et al., 2014) however, this was in the context of a randomised controlled trial (RCT), whereas here it was found that those not in direct contact with HCPs at a study day have the highest DC - implying encountering HCPs and being involved in an RCT in itself could resolve many issues driving DC (Methley et al., 2015), (Mattson et al., 1985). Not unexpectedly, there are additional factors driving DC not directly associated with treatment, and these require further characterisation.

Decision-making is a continuous process and it is necessary to extend these findings into a prospective study, as interaction between perceived disease and treatment risk evolves over time. However, this work offers DC and DR as potential outcome measures to quantify the impact of decisions on pwMS.

In terms of influential parties, there were significant differences observed between cohorts. Partner influence was most significant to the 'on treatment' group. As the entire group were on treatment, partner influence could have been more prominent in their mind. Those least influenced by partners were the 'offered treatment' group but closer inspection of their demographics reveal that this group also had the lowest

number of partners hence there was more significance placed on other close relatives and friends in this group. There was however, no significant difference seen between cohorts with partners. What the result does emphasise is that parties of influence hold different importance to individuals dependent on their life circumstance, and take different forms relative to the cohort observed.

2.9 Conclusion

It has been shown that DC and DR are higher in treatment naïve pwMS and DC is increased in those 'offered treatment' dissatisfied with their current treatment status, whereas those 'on treatment' have low DR. This implies that treatment has an association with lower DC and DR and was confirmed in a multivariate analysis in the total population where DC and DR were increased by dissatisfaction with treatment, lower potency treatment, being employed, being from the 'MS conference attendees' cohort and having more reliance on the doctor's decision.

Furthermore, there was a correlation between treatment satisfaction and DC/DR is only present in those who have been exposed to treatments and not before e.g. treatment naïve patients.

Connected to these findings, in the following chapter, DC is measured across time in an outpatient population being 'offered treatment'. As the outpatient setting is the focus, there are additional measures that interrogate further the patient-doctor interaction viewed as important here across the decisional process.

2.10 Acknowledgements

The thesis author would like to acknowledge the individuals who gifted their time to participate in the research. HCPs as part of the MS service at Imperial College Healthcare NHS Trust allowed access to the patient population without which the research would not have been possible.

2.11 Contribution to work

David Wilkie: Wrote the study protocol and patient documents and obtained all regulatory permissions (ethical and internal and for licensed measurements). Approached all participants and obtained consent and followed up with participants as appropriate. The thesis author entered all data and performed statistical analysis and generating of tables. Organised and performed the interviews and subsequent transcribing and analysis. The thesis author was also responsible for writing the content published as introduction, methods, results, statistical analysis and conclusions sections within the published paper.

Richard Nicholas: Responsible for the analysis of Table 4 and all figures.

Alessandra Solari: Proofreading the manuscript.

2.12 Conflict of Interest

A Solari was board member of Merck Serono and Novartis, and received speaker honoraria from Almirall, Excemed, Genzyme, Merck Serono and Teva. R Nicholas is funded by the Imperial Biomedical Research Centre (BRC) and R Nicholas and D Wilkie are funded by Multiple Sclerosis Trials Collaboration (MSTC).

Chapter 3 Decisions of Uncertainty Broaching Treatment in MS (MS-DOUBT) prospective study

The following chapter has been submitted for consideration in the following journal in an amended form: *Multiple Sclerosis Journal – Experimental, Translational and Clinical* as 'The impact of the face-to-face consultation on decisional conflict in complex decision-making in multiple sclerosis: a pilot study'. With permission of the co-authors (Nicholas and Solari), the information is presented as my own (as lead author) and sentences remain as published (potentially) with additional content as appropriate to the chapter. The paper has been submitted for a Creative Commons by 4.0 licence.

3.1 Introduction

The results of the first two phases of research ('MS conference attendees' and 'on treatment' cohorts) identified a relationship between treatment status and DC. Half of all patients of the combined cohort (n=183) had degrees of DC.

This is of concern because those who identified with DC had potentially unmet clinical needs. As the preceding research was primarily researcher-led and quantitative in nature, the sources of DC were unclear. Having established differences in DC and treatment status in the first two cohorts, and a possible connection to the clinical encounter as resolving issues associated with DC, a prospective study was devised aimed at the outpatient population reviewed by consultant neurologists.

The findings from the 'MS conference attendees and 'on treatment' cohorts therefore informed the development of a standalone study entitled 'Decisions of Uncertainty

Broaching Therapies in MS (MS-DOUBT) (ref: 16/LO/0153). MS-DOUBT is a synonym for the 'offered treatment' cohort referenced previously and interchangeably henceforth.

The main goals of the MS-DOUBT study were to determine what additional factors impacted DC and to investigate how it may be resolved in patients. In addition, to understand the impact of the face-to-face consultation on decision-making and to determine if prerequisites and the process itself could impact on the final treatment decision using DC as the outcome measure.

There are three stages of the decision making process – see figure 10.

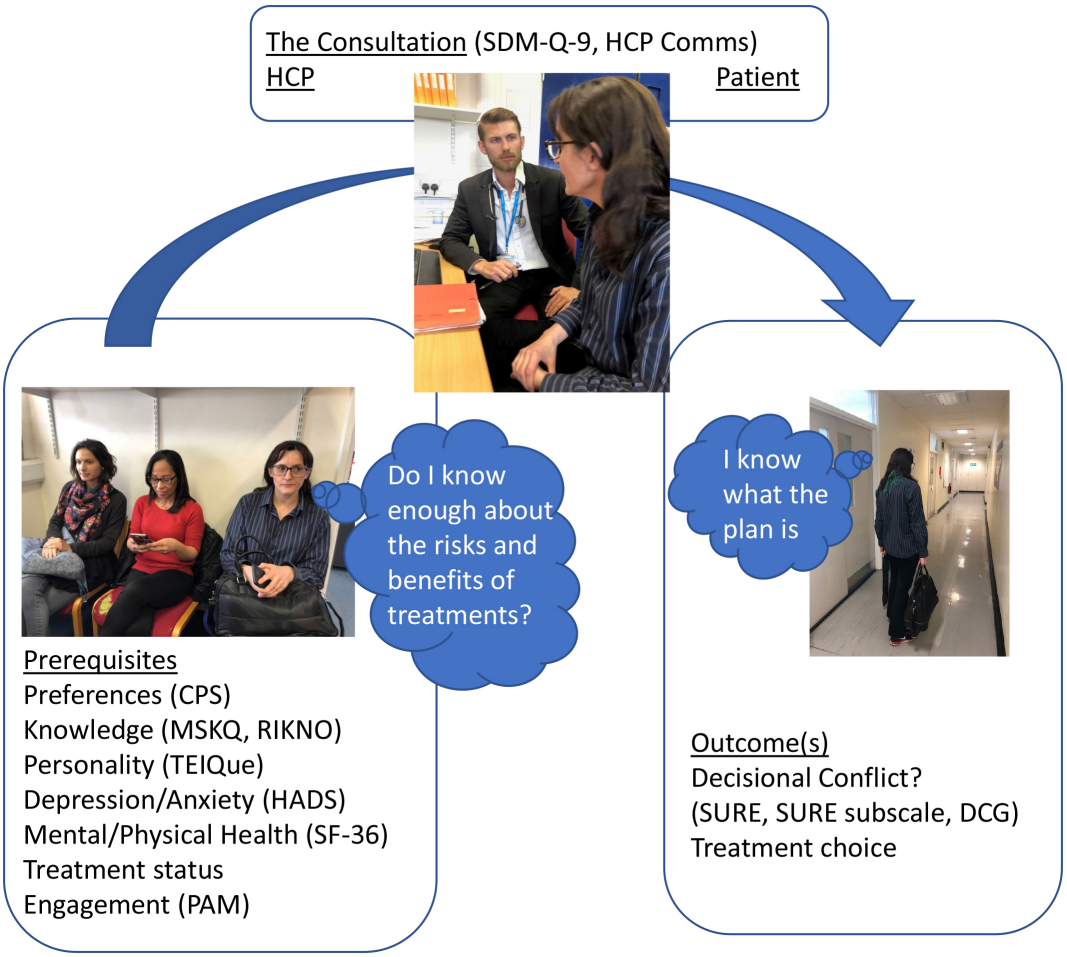

Figure 10: 'The decisional process model: showing the instruments mapped across the decisional process: prerequisites, the consultation and outcome'

Prerequisites e.g. what the patients brings to the consultation, including personality, role preference, mood, readiness to make a decision, and disease and risk knowledge; the process itself e.g. the patient/HCP interaction, best exemplified by SDM, where the HCP and the patient share responsibility for agreeing a way forward. SDM allows people to be supported in understanding their medical condition, utilising treatment and support options whilst evaluating the risks and benefits of each option. It can also elicit a decision about a preferred course of action (Elwyn et al., 2010). Finally, the consultation outcome is key and aims to resolve DC (Heesen et al., 2013).

The role of the face-to-face consultation, in terms of decisions about care, is being challenged. Historically, the HCP would lead on decision-making (Gallagher, 1998) but today, with the aid of the Internet, patients can enter a consultation armed with both preferences and knowledge. Emphasis on self-management in chronic disease and the emergence of the 'expert patient' have questioned the utility of the 'expert' consultation (Gerber and Eiser, 2001). Furthermore, the elements driving a successful and satisfying consultation ultimately leading to a successful decision are opaque, thus how to harness its potential as the healthcare environment becomes ever more complex, is essential to its continuation.

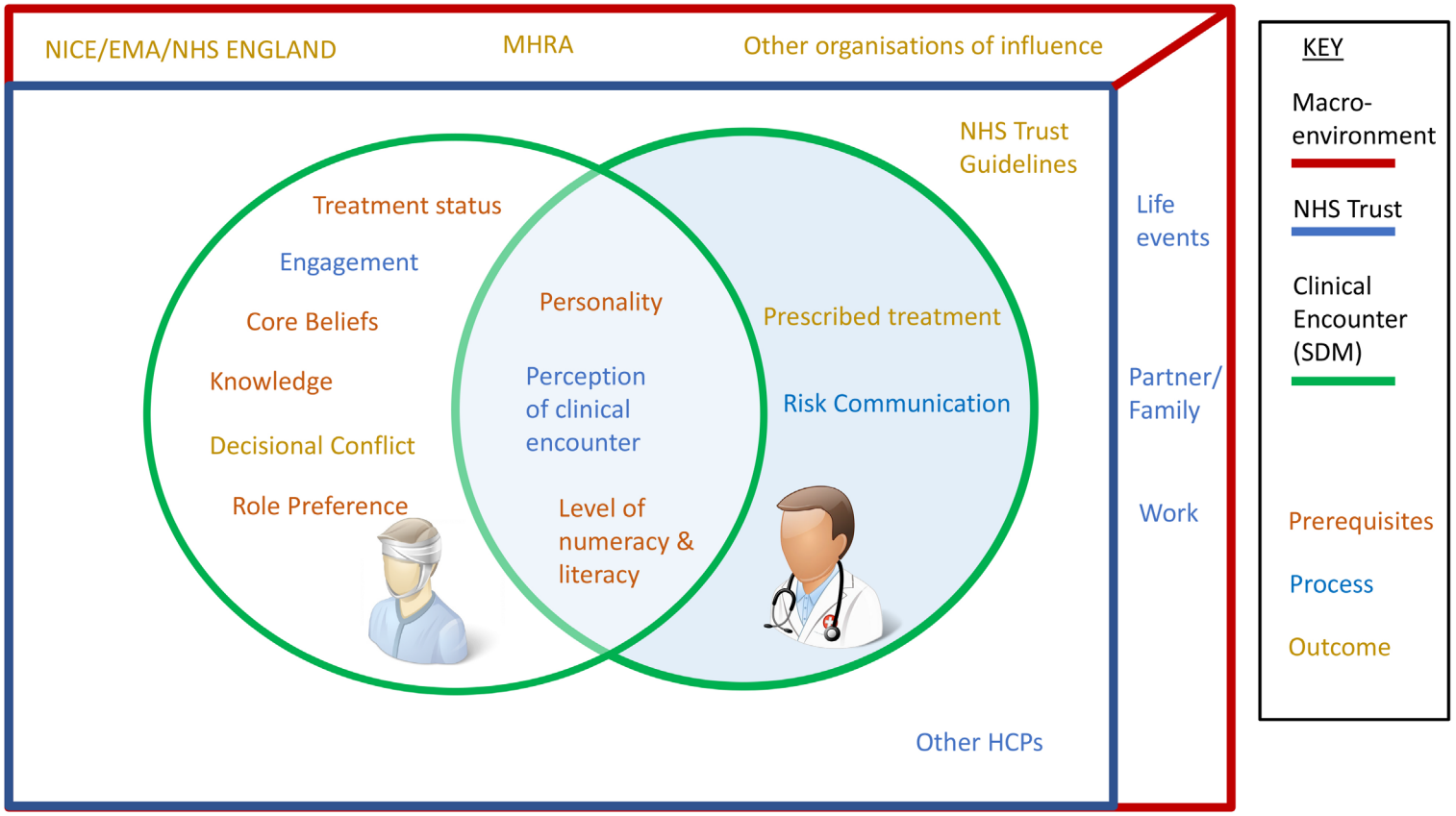

Figure 11: 'Decisional considerations mapped on to environments and defined by decisional process relevant to role'

Figure 11 aims to map the decision-making process on to the clinical environment, acknowledging the greater context of treatment decision-making. In reality choice is further complicated by macro-influences such as organisations that lead on treatment guidelines (NICE, EMA, NHS England), the personality, education and needs of the individual and agreement of the doctor who prescribes. There are non-treatment issues e.g. life events, that can further impact on treatment decision-making.

The MS-DOUBT study employed the same questionnaires used in the previous populations but looked more closely at each stage of the decision-making process, utilising additional measurements. These included emotional intelligence (as a marker of communication skills) and personality traits. A psychometric questionnaire (TEIQue) was used to provide insight into how people make decisions outside of healthcare (Petrides, 2009), (Thomas_International, 2011). Interviews were carried out to help determine external influence and how personal experience (beyond quantitative questionnaires) may subtly or significantly impact on treatment decision-making.

Depression and anxiety is a known component of living with MS and has the potential to impact all areas of life (work, home, self-care, etc) (Sadovnick et al., 1996). This was measured using the HADS scale, which has been used successfully in an MS population previously (Honarmand and Feinstein, 2009). This was further supported by the PAM scale, which tests how engaged and ready a person is to make a decision, the results from which can help to indicate how likely a person will, for example, adhere to a treatment (Insignia, 2015).

As a person's physical status (and notably level of fatigue in MS) could be instrumental in decision-making, the SF-36 questionnaire was used to assess the person's quality of life and if they had symptoms that significantly affect them (Failde and Ramos, 2000). The SF-36 comprises of eight scores (vitality, bodily pain, mental health, social role, physical role, physical functioning and perception of general health (John, 2000), (Freeman et al., 1996) and is self-reported.

In terms of the consultation, a significant finding from the previous two phases of research showed that the consultant neurologist was the most consistent influential party in treatment decision-making. Additional questions were therefore asked of the clinical encounter utilising the SDM-Q-9 and SDM-Q-9-Doc incorporating the viewpoint of the patient and HCP respectively.

Finally, the outcome measure looked at DC utilising three measures to further validate the results. Whether a treatment decision was made and when was also recorded.

3.2 Study Objectives

The broad research aim was to identify a theoretical framework as a basis for developing a decisional intervention with the primary research aim to identify the underlying conditions that support and influence treatment decision-making in pwMS. In addition, to understand the impact of a face-to-face consultation on decision making and to determine if prerequisites and the process itself could impact on the final treatment decision, using DC as the outcome measure.

For the secondary aims listed, the aim is demonstrated followed by the intended means for achieving the aims in brackets.

3.2.1 Secondary aims:

 To explore personality and emotional traits of pwMS and how these factors may underpin the decision-making process (method: TEIQue).

 How decision-making is applied outside of the healthcare setting using the factors described (method: factors and parties of influence, interviews).

 To establish factors resulting in high DC in the MS population (method: DC outcome measures).

 To identify areas of service and treatment priority relevant to decision-making. (method: interviews and treatment factors).

 To investigate how DC may be resolved in those with no DC in the MS population (method: follow-up cohort at year 1).

 To examine how decision-making changes over time (method: follow-up cohort at year 1).

3.2.2 Tertiary aims:

 To further validate existing measurements and constructs in pwMS and to determine correlation (methods: all instruments).

 To investigate how information is processed differently by individuals (aptitude and knowledge) (methods: MSKQ, RIKNO, TEIQue).

3.3 Study Design

The study employed a sequential explanatory mixed-method design incorporating quantitative questionnaires and analysis and semi-structured interviews with qualitative analysis. This study design was chosen because each research stage would inform the direction of the next. A study protocol formalising the research aims and methodology was developed by the thesis author and ethical approval sought. Data analysis was performed in tandem with data collection by the thesis author.

3.4 Ethical approval

Ethical approval for the study was achieved through London-Harrow Research Ethics Committee (16/LO/0153).

3.5 Methods

3.5.1 Questionnaires

Section 1: incorporated demographical and disease information, including: gender, age, ethnicity, marital status, employment status, academic achievement, salary level, MS type and year of diagnosis. The section also incorporated broader views such as religion and political persuasion. This was achieved by looking at official sources such as the Office for National Statistics to determine how variables were grouped and questions have been developed over time for e.g. census questionnaires (ONS, 2020). In addition, guidance was sought from Survey Monkey which had established surveys with broad application (Survey_Monkey, 2020).

***Section 2*:** incorporated questions about factors influential to selecting treatment including route and frequency of administration, efficacy, side effects, risk factors and pregnancy (or desire to start a family). An additional question was added to establish if the patient had existing children in order to inform the low significance of pregnancy as a treatment factor in the preceding research.

Section 3: incorporated the five-item DRS (Brehaut et al., 2003), (O'Connor, © 1995 [updated 2010]) to ascertain if DR was present referencing current treatment status.

Section 4: listed influential parties including consultant neurologist, partner, other close relatives, friends to employer and religious (or faith) leader (as applicable). Additional parties that may hold significance were added: physiotherapist, occupational therapist and MS specialist nurse. The patient then marked on a Likert scale the level of significance to them. It was expected that some of these additional

parties may hold additional importance depending on the time-point in the disease course.

Section 5: introduced the respondent to clinical scenarios using the CPS (Solari et al., 2013).

Section 6: HADS scale, a measure of anxiety and depression (Zigmond and Snaith, 1983), (Honarmand and Feinstein, 2009).

***Section 7*:** PAM measurement, testing how engaged and ready a person felt they were to take action (Insignia, 2015).

Section 8: TEIQue questionnaire, used to gain a better understanding of the person's individual emotional and personality traits (Petrides, 2009).

Section 9: RIKNO questionnaire to determine the patient's treatment risk knowledge (Heesen et al., 2017)

Section 10: SF-36, a measurement of the patient's health status and levels of fatigue (Ware et al., 2008).

See Appendix C for questionnaires.

In the following section, ordered as listed in figure 10, the measurements and instruments used are described further.

3.6 Prerequisites

3.6.1 Preferences

3.6.2 Control Preference Scale (CPS)

The CPS was previously described in chapters 1 and 2. The CPS comprises of five cards portraying a scenario involving treatment decision-making. Each card presents a different cartoon and statement including a preference for an active, autonomous role, sharing the decision with physician through to a passive role whereby the physician leads on the decision (Solari et al., 2013). In this context, the patient was asked to record their first preference.

3.7 Knowledge

3.7.1 Multiple Sclerosis Knowledge Questionnaire (MSKQ)

The MSKQ is a 25-item multiple-choice questionnaire testing a person's disease knowledge (Giordano et al., 2010), (Borreani et al., 2011). As this is an Italian-derived measure, it was adapted for a UK audience following discussion with supervisors e.g UK MS rate replacing the Italian equivalent being the only change made. A higher number of correct scores indicates greater knowledge.

3.7.2 Risk Knowledge in Relapsing Multiple Sclerosis (RIKNO)

The RIKNO questionnaire is a 21-item multiple-choice questionnaire used to determine a patient's level of risk knowledge as a prerequisite for SDM. It has been used formerly in those with newly diagnosed with RRMS (Heesen et al., 2015). It was adapted a second-time (used here) (Heesen et al., 2017). As with the MSKQ, a higher number of correct scores indicates greater knowledge.

Participants were discouraged from using phones or computers to research answers, for example by going to sources of information such as the Internet.

3.8 Personality

3.8.1 Trait Emotional Intelligence Questionnaire (TEIQue)

The TEIQue is a 153-item questionnaire based on emotional intelligence theory and has been psychometrically validated in a number of studies (Petrides, 2009). The user is asked to complete the test as quickly as possible *with seven possible responses, ranging from* 1=Completely Disagree to 7=Completely Agree based on statements. Example statements include: *"I get stressed by situations that others find comfortable"* or *"I really don't like my physical appearance".*

The questionnaire explores people's beliefs about their emotional abilities (how good they consider themselves in identifying, understanding, and managing their own emotions and that of other people's emotions). These beliefs are used as predictors of interpreting a range of other behavioural traits including self-esteem, management of stress, assertiveness, empathy, optimism, self-motivation, emotional management and expression as part of fifteen sub-scales (Petrides, 2009). The test generates a score across the categories described with a factor score (incorporating other facet variables) ranging from Well-being, Sociability, Emotionality and Self Control. For example, Optimism comes under 'Well-being' and Assertiveness under 'Sociability'.

A percentile score is generated from the scores within each facet which can then be combined to generate a global score that fall within a range relative to normative levels

of 30-69%. Anything outside of this range is considered below average (1%-29%) or above average (70%-99%) (Thomas_International, 2011).

To the knowledge of the thesis author, the TEIQue had not been tested on an MS population previously.

3.9 Depression/Anxiety

3.9.1 Hospital Anxiety and Depression Scale HADS)

The Hospital Anxiety and Depression Scale (HADS) was developed to detect symptoms of anxiety and depression in patients (Zigmond and Snaith, 1983). It has since been used and validated in the MS population (Honarmand and Feinstein, 2009). An example question relating to the anxiety component of the questionnaire is *'I get sudden feelings of panic'*. An example question relating to the depression side of the questionnaire is '*I have lost interest in my appearance*'. The respondent then selects one answer from multiple choice answers to what degree (if at all) the statement applies to them. Each item is scored from 0-3 resulting in a total score between 0 and 21 for anxiety or depression (higher scores representing greater severity) (Atkins et al., 2012), (Breeman et al., 2015).

3.10 Mental/Physical Health

3.10.1 Short Form 36 Health Survey (SF-36)

The SF-36 is considered to be a dependable measure of a person's health status (Failde and Ramos, 2000) and has been used extensively in the MS population previously (Vickrey et al., 1995), (Hobart et al., 2001). Domains tested include: physical function

(and limitation), general health, body pain, social functioning, role limitation due to emotional issues as well as mental health. (Rothwell et al., 1997), (Kappos et al., 2014). No overall score is generated; instead, the subscales described contribute separate summary scores for the physical and mental health components. Scores range 0-100 with higher scores indicating less disability (Ware, 2008).

3.11 Treatment status

As per Chapter 2, this is a measurement of the person's current treatment status: on or off treatment and whether they are considering treatment options or not.

3.12 Engagement

3.12.1 Patient Activation Measure (PAM)

The PAM is a commercially licensed measurement of patient activation. PAM measures where a person lies within four levels of motivation encompassing self-reported health-management, confidence and knowledge (Hung et al., 2013). The patient is asked to score their level of agreement across a likert scale and this generates a score indicating how a patient can be best supported. For example, a point increase in PAM score has been shown to correlate to a 2% decrease in hospitalization and the same percentage increase in treatment adherence (Insignia, 2015). The levels are defined as firstly Level 1: 'Disengaged and overwhelmed'; Level 2: 'Becoming aware, but still struggling'; Level 3: 'Taking action'; Level 4: 'Maintaining behaviours and pushing further' is characterised by an adoption of new behaviours and focus on healthy lifestyle. People at level 4 may still be influenced by life struggles but generally they are their own health advocate (Insignia 2015).

3.13 The Consultation

3.13.1 Shared Decision Making-Questionnaire (SDM-Q-9)

The SDM-Q-9 for both the patient (SDM-Q-9-patient) and doctor (SDM-Q-9-doc) was incorporated in order to determine the viewpoints and perception of the clinical encounter of both the patient and neurologist directly following the consultation.

Example statements (consistent across both questionnaires) include:

'*My doctor made clear that a decision needs to be made'* or *'My doctor told me that there are different options for treating my medical condition'.*

The respondent than has multiple-choice answers to choose from on a scale from 'completely disagree' to 'completely agree'. The answers are then compared (HCP to patient) to determine consensus/agreement across each item (Kriston et al., 2010).

An additional box was added by the thesis author to the SDM-Q-9-doc questionnaire to record the patient's Extended Disability Status Scale (EDSS) as a measurement of a person's ambulation and functional systems. The patient is scored between 0-10 in 0.5 increments determined by neurological exam, where 0 represents no neurological deficit and 10 is death due to MS (Kurtzke, 1983), (Hatipoglu et al., 2016).

3.13.2 Clinical Encounter ('HCP comms')

'Clinical encounter' was communicated in terms of seven questions that were used to generate a communication or 'HCP comms' score (Croker et al., 2013), (Roberts et al., 2014). The user was asked: thinking about your most recent consultation at Charing

Cross Hospital with the consultant neurologist, how good was the doctor at each of the following? Please select one choice for each row.

The questions about the HCP included: '*giving you enough time', 'asking about your symptoms', listening to you', 'explaining tests and treatments', 'involving you in decisions about your care', 'treating you with care and concern', 'taking your problems seriously'*.

The second question, 'HCP confidence', addressed how confident the patient was with the HCP seen (definite, partial or no confidence) in response to the question '*Did you have confidence and trust in the doctor that you saw?'*. These were analysed as per author instructions (Croker et al., 2013), (Roberts et al., 2014). See statistical analysis section.

This information was supported by inclusion of the measurement of the clinical encounter described in Chapter 2. The rationale for including this was to determine additional factors that may contribute e.g. time during consultation, confidence and trust in the doctor, not captured by the SDM-Q-9.

Using clinical notes, the cohort was further divided by time of treatment decision: pre-baseline ('past'), at 'baseline' and those who deferred to post-baseline i.e 'future' group.

3.14 Outcomes

3.14.1 Decisional Conflict (SURE, SURE-Subscale and DRS)

The individual's level of DC was measured using the SURE scale , a variant of the DCS described previously in chapter 2. For the SURE subscale - each question of the SURE scale was summed (scored 0-4 indicating range of DC with 0-3 indicative of DC (0 being the highest DC) and 4 representing No DC (Légaré et al., 2010a). A visual analogue scale created by the author in the DCG asked the participant to arbitrarily mark on a scale (0-100) where their DC lay. The purpose of this approach was to determine degrees of DC: none to severe - 100 being the most severe. The scale was based on previous visual analogue scales that have been used to describe pain severity, but in this case severity was applied to DC (Heller Gillian et al., 2016).

3.14.2 Treatment choice

Whether a person followed through on the intention to have treatment was measured at baseline and as part of the follow-up cohort (SDM-Q-9) referencing their own treatment intention as well as information recorded in clinical notes by the HCP(s).

3.15 Interviews

Study participants were contacted within six months of their clinic date and invited to interview. These were organised by entry into the study and by availability. It was determined that the 'first come' approach described would overcome some elements of bias as the patients could not be handpicked using this method. A limitation of this approach was that it meant that the population could not be stratified. It was anticipated as the research progressed, that some discrepancies in representation could

be overcome. However, due to the nature of thematic analysis, the research concluded once themes had been identified and exhausted. It would have been unethical to continue collecting patient data that would not have added to the research for the purpose of representation.

The interviews were semi-structured and recorded. The resulting transcripts were typed by the thesis author and analysed using thematic analysis. When no new themes emerged, the interviews ended.

As there is evidence to support that interviews conducted at home can relax the patient and enrich the data (Holloway and Wheeler, 2010), this approach was preferable and seven of eight interviews occurred in the home of the patients. In addition, it was possible to record physical responses using this method; one interview occurred in the hospital and was a follow-up interview with the same patient a year later to determine if any additional themes had emerged since baseline. No telephone interviews were conducted.

Patient interviews were led by a semi-structured script (see appendix D) based upon the data that emerged from the individual's questionnaires. Broadly, interviews covered the following themes:

Behavioural and Personality traits

eg. The results of the patient's own TEIQue were discussed in detail (including decisions made outside of healthcare) to determine areas of agreement and disagreement.

Disease management

eg. To develop an understanding of how a person manages their disease medium to long-term (eg. personal and work-related life plans and goals) to short term considerations that can be variable (eg. impact of fatigue).

Support & Understanding

eg. Participants were asked to describe the MS services that they use eg. hospital, friends and family, work, to online resources.

Influence

Who are the most influential parties in a person's life and what influences(s) do they exert?

What are the main treatment priorities and how might these change over time?

Knowledge & Experience

How have treatment decisions now been informed by past experience?

In what ways can information about treatments be challenging to understand or interpret?

3.16 Statistical Analyses – Quantitative

Analysis of the demographics was performed as previously described in Chapter 2. Raw values were used for regression analysis unless otherwise stated; some further data conversions were made for T test comparison and are referenced as appropriate.

For the SURE scale (Légaré et al., 2010a), DC was recorded as 1=DC and 0=No DC. For the SURE subscale each question of the SURE scale was summed (range 0-4) as described in methods. For the DCG, the score was taken from the line indicated by the participant on the visual analogue scale (0-100).

The HADS score was re-categorised into Normal (scores 0-7), Mild (8-10), Moderate (11-14), Severe (15-21) (Atkins et al., 2012), (Breeman et al., 2015)

The SDM-Q-9 score was generated by summing the individual scores across the nine questions, multiplying by 20 and dividing by nine. This generated a score between 0-100 where a higher score was indicative of SDM occurring. (Kriston et al., 2010). This questionnaire was completed by patients.

The SDM-9-Doc score was generated by summing the individual scores across the nine questions, multiplying by 20 and dividing by nine. This generated a score between 0-100 where a higher score was indicative of SDM occurring. (Kriston et al., 2010). This questionnaire was completed by neurologists.

For the MSKQ, the score was summed by the total number of correct answers possible (Giordano et al., 2010).

For the RIKNO, the score was summed by the total number of correct answers possible (Heesen et al., 2015).

CPS was adapted with permission of the lead author in Solari, its main purpose, under these conditions, is to gain a better understanding of the patient's first preference only;

thus answers were re-coded as 1=Active 2=Active-Collaborative 3=Collaborative 4=Passive-Collaborative 5=Passive.

The TEIQue (Petrides, 2009) was independently marked by Thomas International as per the licensing agreement generating scores across the facets which were categorised by values 1-29 (below average), 30-69 (average) and 70-99 (above average) (Thomas_International, 2011).

The Clinical Encounter score was generated by summing the individual scores across the seven questions (1=Very Poor, 2=Poor, 3=Neither good nor poor, 4=Good, 5=Very Good) multiplying by 20 and dividing by 7 (Croker et al., 2013) or multiplying by 25 and dividing by 7 with 0=Very Poor up to 4=Very Good (Roberts et al., 2014) as per other author instructions in order to obtain the mean score for comparison. Missing items were averaged based on other scores generated by the same individual.

HCP was categorised as 'Richard Nicholas' or 'Other' and HCP Confidence as 'yes to some extent or no confidence' or 'yes, definitely' as per author instructions (Croker et al., 2013).

PAM scores were independently marked by Insignia as per the licensing agreement – producing raw scores that were then converted to activation levels 1-4 (Insignia, 2015).

SF-36 scores were independently marked by Optum as per the licensing agreement producing raw scores for analysis. These scores were entered by the thesis author for

further interpretation using Optum-supplied software converting the raw scores as below average (0-49), average (50) or above average 51-100) (Optum, 2019).

Data is presented as ratios, percentages and means and standard deviations where appropriate. Statistical analysis was performed using the paired T-test, two-way ANOVA (GraphPad Prism, version 7.02 September 2016: www.graphpad.com). Categorical data was analysed using x2 and Fishers exact test (Vassarstats: www.vassarstats.net accessed 06/08/2019) where appropriate. Modelling the dependence of the scores (DC, SDM) on the covariates was performed using linear and logistic regression models using SPSS (version 22). In logistic regression, covariates were described as odds ratios, reported with 95% confidence intervals and p values testing the null hypothesis of no effect. Graphs were drawn using SPSS, Version 22 and GraphPad Prism (version 7.02 September 2016: www.graphpad.com). All multi-variate analyses were performed using the 'enter' method.

3.17 Statistical analysis - Qualitative

Analysis of the data was informed by thematic analysis (Braun and Clarke, 2006). Thematic analysis is a phased approach looking for themes in data. A theme embodies elements important within the data in response to the question being asked. There is no consensus on an agreed approach to thematic analysis so its application varies. However, Braun and Clarke (2006) outline a six-stage approach. The approach starts with familiarisation of the data which involves repeat-reading and to gain a general overview of what the person is relaying. The second phase involves recording codes or finding the 'gist' of the sentence or paragraph in an abbreviated form. The third

phase involves grouping the codes into themes. The fourth phase involves the refinement of the themes as there can be crossover, or to determine if some themes can be dismissed or created; the penultimate phase looks at the themes more closely to determine what is *really* being relayed or the direction of the content within the theme created. The final stage is an analysis or reporting of the theme (the story or narrative) for the purpose of publication (Braun and Clarke, 2006).

Interviews were recorded with permission of the patient and later transcribed by the thesis author. Next, the data was read and re-read to determine if any themes jumped out. This was determined by the interviewee spending greater time on a subject or returning to the same subject more than once. There was a limitation in the interviews being semi-scripted, so to a degree the participants were being led to subjects of interest. However, this was off-set by the fact that responses could not be known and thus, once several transcripts had emerged, the consistency in the question structure allowed for themes in the answers to be identified more easily. A theme became more significant if the same person referenced it multiple times or several people referenced it in a similar context e.g. the presence of a partner at appointments was often referenced without prompt on the side of the author.

3.18 Sample Size

The study sample size (n=60) was informed by the sample sizes of the 'MS conference attendees' and 'On treatment' cohorts and factoring a response rate of 50% from a larger sample of people to approach (n=120). In addition, it was proposed that a larger sample would support selection of a sufficiently homogeneous

sample for subsequent stages of research and to factor potential drop-outs. From this larger sample of participants it was proposed that groups could be stratified by DC severity.

Initially the entry criteria required that people score within the upper quartile of the DCG married to all DC answers being ticked 'no' as measured by the SURE scale (indicating extreme DC). The opposite applied to those with no DC (lowest quartile and no-DC). A high DC group was to be identified from the larger cohort (n=40) on the basis that they would have the highest clinical need and determining the conditions that underpin DC being a key area of focus. This was to be balanced by the low DC group (n=20) to explore how DC may be resolved. However, the circumstances of most people approached fell somewhere in-between, reflective of the true picture of the decisional process. For this reason, an amendment was sought from the ethics committee and subsequently approved in order to make the entry criteria less stringent as it became apparent from the early stages of recruitment, that people were being lost to the process and the groups could be stratified at the end of the process to determine DC severity using the DC outcome measures (see section 3.14.1).

The interview sample size (up to n=30) was calculated from the recruited group and factored a 50% drop-out rate. The interview number proposed was provisional and the number was expected to reduce as determined by the themes that emerged from the analysis stage. When all themes were identified and no new themes emerged, the research was thus considered complete.

A literature review indicated no universal consensus on how many interviewees are deemed appropriate to this type of research (Baker and Edwards, 2012), (Sargeant, 2012), however, the number proposed was further supported by experts in the field (psychologists at Surrey University, thesis author's supervisors).

3.19 Results - Quantatitive

High levels of DC is associated with less confidence in healthcare decision-making

Seventy-three of one hundred and twenty nine pwMS (57%) approached immediately after their usual MS specialist consultation took part (see figure 12). The demographics of those who gave informed consent are presented in Table 6, split by DC status.

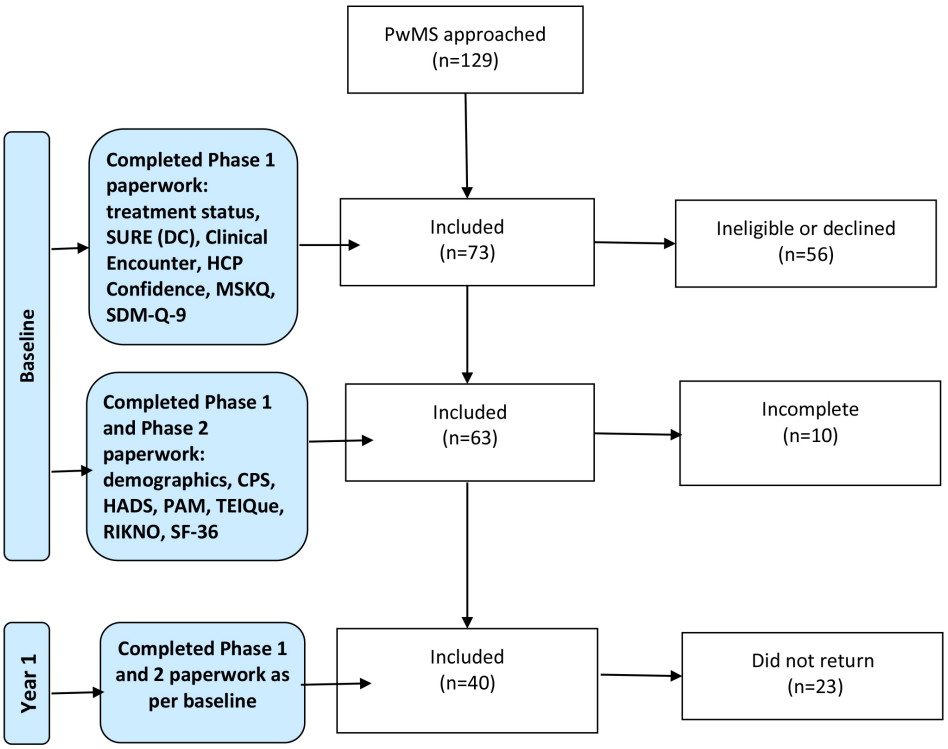

Figure 12: 'Flow-chart of patient participation per study phase showing questionnaires completed'

Table 6: Baseline characteristics (general, clinical, prerequisite of the decisional process, and consultation outcomes) of the MS-DOUBT cohort by DC.

There were the following missing data: marital status (n=10), employment (n=7), time from MS diagnosis (n=4), ethnicity (n=1), disease type (n=1).

Characteristic	DC present (n=39)	DC not present (n=34)	P value
	N (%)		
Women	33 (58.9%)	23 (41.1%)	NS
Age 18-44 years	19 (48.7%)	21 (61.7%)	NS
White ethnicity	30 (78.9%)	29 (85.3%)	NS
With partner	20 (60.6%)	13 (43.3%)	NS
Employed	26 (76.5%)	19 (59.4%)	NS
Relapsing MS	35 (92.1%)	33 (97.1%)	NS
MS diagnosis 0-3 years	17 (45.9%)	15 (46.9%)	NS
EDSS score 6.0 or above	8 (14.2%), 11 missing	4 (24.2%), 1 missing	NS
MS Knowledge (MSKQ)*	39, 16.56, 4.756	34, 17.12, 3.506	NS
Risk Knowledge (RIKNO)*	32, 7.06, 3.793	28, 7.21, 3.119	NS
SF-36: Physical Status* Mental Status*	32, 43.53, 9.867 32, 46.03, 11.743	29, 44.48, 10.716 29, 48.10, 9.518	NS NS
HADS: Anxiety* Depression*	31, 8.84, 4.691 31, 4.90, 3.673	30, 7.00, 3.051 30, 4.40, 3.255	NS NS
TEIQue: Overall Score* Adaptability*	31, 4.7739, .56797 31, 4.0177, .85866	24, 4.9011, .54324 24, 4.1013, .98937	NS NS
CPS Active/collaborative role	16 (48.5%)	18 (58.1%)	NS

Healthcare Management (PAM)*	38, 50.3684, 25.43657 (raw) 38, 2.29, 1.011 (by level)	34, 60.5735, 22.89751 34, 2.88, 1.094	NS=0.077** 0.02
DMT history: Treatment naïve Off treatment On treatment	17 (43.6%) 10 (25.6%) 12 (30.8%)	9 (26.5%) 12 (35.3%) 13 (38.2%)	NS
Not satisfied with treatment	32 (82.1%)	27 (79.4%)	NS
SURE Subscale*	39, 1.69, 1.104	34, 4.00, .000	N/A
Decisional Conflict Gauge*	39, 64.77, 17.426	34, 32.56, 32.561	NS

* Number, Mean, SD
**NS=Not Significant but included to show trend
N/A=Not Applicable

During the consultation it had been made clear a clinical decision about treatment needed to be made - unrelated to the study. Fifty-nine (81%) were 'not satisfied' with their current treatment status. Thirty-nine of 73 (53%) had DC and 32 of the 39 (82%) were also 'not satisfied' with their current treatment status.

The stages of the decision process was mapped initially by assessing the patient's prerequisites, then interrogating the consultation from both the patient's and HCP's perspective and finally determining the subsequent outcome of the meeting (Figure 10). A multivariate analysis was performed with all the prerequisites (Table 7). Those with less confidence in their healthcare decision-making (PAM) were more likely to have DC using all three measures of DC (n=72, SURE scale [adjusted R^2 0.06, p=0.02]; (n=72, SURE-subscale [adjusted R^2 0.04, p=0.04]; (n=72, DCG [adjusted R^2 0.04, p=0.04]).

Table 7: Multivariate analysis of factors associated with the SURE scale measure of DC, SURE-Subscale, DCG, SDM and HCP confidence

Multivariate analysis of factors associated with the SURE scale measure of DC, SURE Subscale, DCG and SDM. The SURE scale - as the primary measure - was used as a dependent variable and run against the co-dependents described. The SURE sub-scale and DCG were used to support the findings of the SURE scale. The following co-dependents were used: Treatment Status, MSKQ, RIKNO, SF36 (inc. Physical & Mental), TEIQue (overall score), HADS (Anxiety & Depression), CPS, PAM, SDM, Clinical Encounter or as otherwise stated. Those emboldened are significant.

	β, (95%CI lower, upper), p							
Factor	**SURE scale (n=72)**	**SURE scale (n=67)**	**SURE Subscale (n=72)**	**SURE Subscale (n=68)**	**DCG (n=68)**	**DCG (n=68)**	**SDM (n=68)**	**HCP confidence**
Co-dependents (prerequisites)	Treatment Status, MSKQ, RIKNO, SF36, TEIQue, HADS, CPS, PAM.	Treatment Status, MSKQ, RIKNO, SF36, TEIQue, HADS, CPS, PAM.	PAM	PAM	PAM	PAM	Treatment Status, MSKQ, RIKNO, SF36, TEIQue, HADS, CPS, PAM.	-
Co-dependents (consultation)	-	**SDM, Clinical Encounter**	-	**SDM**	**-**	**SDM**	**Clinical Encounter**	**Clinical Encounter**
PAM	-.127 (-.233, -.021), 0.020	-.094 (-.184, -.003), 0.04	.312 (.010, .614), 0.04	-	-6.698 (-13.168, -.228), 0.04	-	-	-
SDM	-	-.012 (-.016, -.008) 0.00	-	.041 (.030, .051), 0.00	-	-.532 (-.816, -.248), 0.00	-	-
Clinical Encounter	-	-	-	-	-	-	.985 (.552, 1.418), 0.00	-

Asking about your symptoms	-	-	-	-	-	-	-	.167, (.017, .318), .030
Listening to you	-	-	-	-	-	-	-	-.324, (-.629, -0.19), .037
Treating you with care and concern	-	-	-	-	-	-	-	.196, (.008, .384), .041
Taking your problems seriously	-	-	-	-	-	-	-	(.284, .050, .517, .018

Optimal SDM is associated with less DC

Moving on to the consultation, 86% had definite confidence in their MS specialist; the remainder reported partial confidence with no one reporting no confidence. Overall, one HCP (of a total of five HCPs taking part) saw 53/73 (73%) of all patients. This HCP also received a higher HCP satisfaction score over colleagues: 50/53 (94%) with definite confidence in this doctor vs. 13/20 (65%) in the 'others' group (p=0.003). The main themes of the consultation that the patient classed as relevant were consideration of 'Asking about your symptoms', 'Listening to you', 'Treating you with care & concern' and 'Taking your problems seriously' (Adjusted R^2 .316, p=0.000). See table 7.

From the patients' point of view, the overall perceived level of involvement, trust and confidence in the consultation was similar to the General Population (Table 8).

Table 8: Patient prerequisites of the decisional process and features of the Clinical Encounter.

Prerequisites patients bring to the consultation					
	Study population		**Comparator population (ref)**		
Measurement (Instrument)	**N**	**Mean,SD (range)**	**N**	**Mean, SD**	**P value**
MS Knowledge (MSKQ)	73	16.8, 4.2 (3-25)	90 **(1)**	10.2, 3.2	<0.0001
Risk Knowledge (RIKNO)	60	7.1, 3.5 (0-15)	1939 **(2)**	8.7, 3.5	0.001
Physical Status (SF-36)	61	44.0, 10.2 (21-63)	126 **(3)**	46.0, 10.1	NS
Mental Status (SF-36)	61	47.0, 10.7 (20-68)	126 **(3)**	48.5, 10.1	NS
Anxiety (HADS)	61	7.9, 4.1 (2-20)	144 **(4)** 1792 **(5)**†	8.6, 4.4 6.14, 3.76	NS 0.0009
Depression (HADS)	61	4.7, 3.4 (0-12)	144 **(4)** 1792 **(5)**†	5.9, 3.5 3.68, 3.07	0.02 0.02
Overall Score (TEIQue)	55	39.0, 24.0 (1-94)	1721**(6)**† 542 **(7)**†	50.0, 20.0 36.7, 12.0	NS NS
Adaptability (TEIQue)	55	28.3, 23.0 (1-98)	1721 **(6)**†	50.0, 20.0	<0.0001
Role Preference (CPS)	64	1.6, 0.7 (1-5)	23 **(8)**	1.8, 0.7	NS
Healthcare Management (PAM)	72	55.2, 24.6 (0-100)	199 **(9)**	63.2, 11.9	0.01
The Conversation: features of the consultation					
Clinical Encounter	73	89.7, 11.5 (57-100)	7429 **(10)** ††	87.5, 17.8	NS
Shared Decision Making (SDM-Q-9)	68	31.2, 10.6 (3-45)	221 **(11)**	38.7, 8.5	<0.0001
Shared Decision Making (SDM-Q-9-Doc)	62	39.2, 6.5 (18-45) ††† 87.2, 14.5 (40-100)	10 **(12)** ††††	80.2, 19.7	NS

See table 8 references.
† General population, †† Non-MS, ††† This value has been converted again as per the author's instructions (12) to enable comparision to non-MS group, †††† Non-MS group with depression

Prerequisites: knowledge; physical and mental health, personality and engagement

In this MS group, knowledge of MS and treatment risk were positively correlated ($n=60$, $R^2=0.261$, $p<0.0001$), however, knowledge of MS was better than expected for pwMS (Table 8, line 1) but risk knowledge was lower (Table 8, line 2). Comparing the MS group to the General Population, there were no differences in mental or physical health (SF-36); though the group had less depression and anxiety than a comparator MS population but more depression than the General Population (Table 8, line 6). As a whole the MS group favoured an active-collaborative role (Table 8, line 9) but they were significantly less engaged than a comparable MS group (Table 8, line 10). All personality and behavioural scores across facets were within normal range with the exception of 'adaptability' (see Figure 13, over-page).

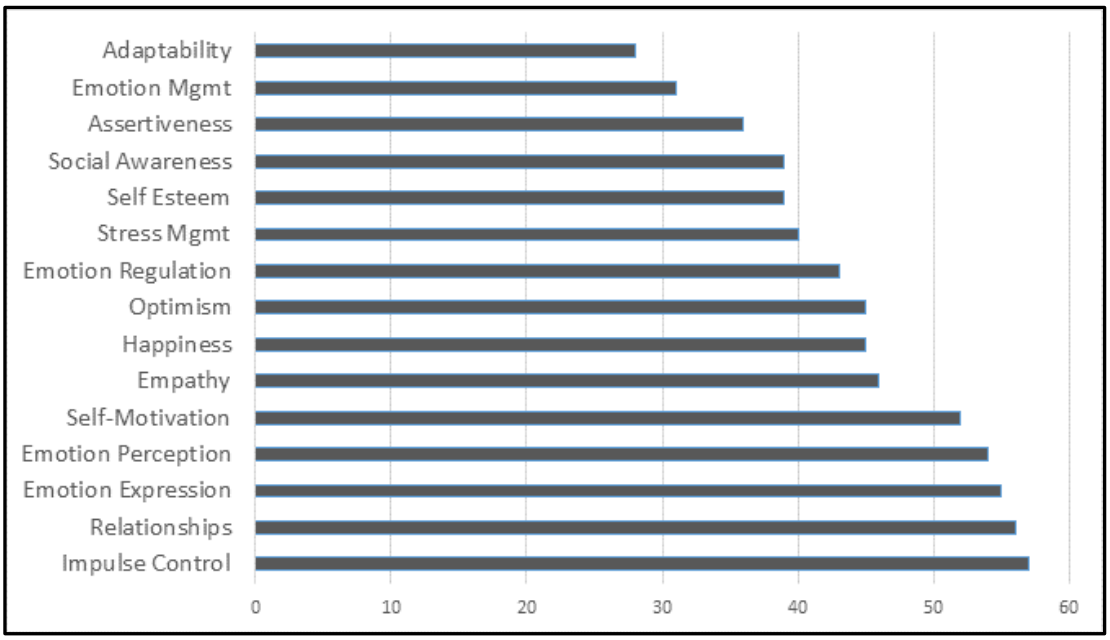

Figure 13: Personality and behavioural facets of the MS-DOUBT population'

All personality and behavioural trait scores were within the normal range (30-69) with the exception of Adaptability which was scored <29. This was significantly different from the General Population (p=<0.0001, Table 8, line 8) meaning this MS group were less adaptable than the General Population (Petrides, 2009), (Thomas_International, 2011).

SDM assessment was performed by both patient and doctor post-consultation. The patients' SDM score was lower than a comparator MS population (Arroyo et al., 2017). The doctors' SDM assessment reported that the doctor perceived there was significantly more SDM during the consultation than the pwMS identified (for pwMS: SDM-Q-9 69.4, for drs: Q-9-doc 87.21+SD, p=0.0000; Table 8). A multivariate analysis was performed for DC, using the same prerequisites described in Table 8, but this time including the consultation variables (Table 7). When the summed SDM raw scores were added to the models predicting DC, SDM was a significant factor for DC alongside PAM (n=67, SURE scale [adjusted R^2 0.38, p=0.000]; and SDM was a

standalone driver using SURE-subscale (n=68, [adjusted R^2 0.44, p=0.000]); DCG (n=68, [adjusted R^2 0.16, p=0.000]). This implied that patients who felt more involved in the process of decision-making also had lower DC.

Good communication is associated with successful SDM

When the SDM score was isolated as a dependent variable and run against the same prerequisites as the DC analysis, the clinical encounter score was the only variable that came out as a significant driver of SDM (n=68, adjusted R^2 0.23, p=0.000). This shows that better communication scores as perceived by the patient during their consultation are associated with successful SDM. There was consensus in 54/72 (74%) when the patient's treatment choice [e.g start, end, continue, change], was compared to the viewpoint of the doctor's following consultation, but consensus itself was not associated with DC or SDM measures.

The final decision arising from the consultation

Overall, 51/73 (70%) of people made their decision at the baseline consultation (41/73, 56%) or reinforced a former decision (10/73, 14%) in the consultation. In the remainder (19/73, 26%), analysis of patient records was used to identify when a decision was made. There was a mean of 29 ±58 days (median of 0 days) from the initial consultation to a recorded intention to treat (Figure 14) with all but 3/73 (4%) following through on the decision by 308 days of the baseline appointment. Given the association of low PAM with less SDM and more DC, those who made a decision before or in the consultation (n=51, 'past/baseline' group) and those after (n=19, 'future' group) were studied. The 'future' group had lower PAM scores

though not significant (8/18 [45%, 1 missing] vs 32/51 [63%], p=0.28) and a trend to have more DC (14/19 (74%) versus 'past/baseline' 23/51 (45%), p=0.057).

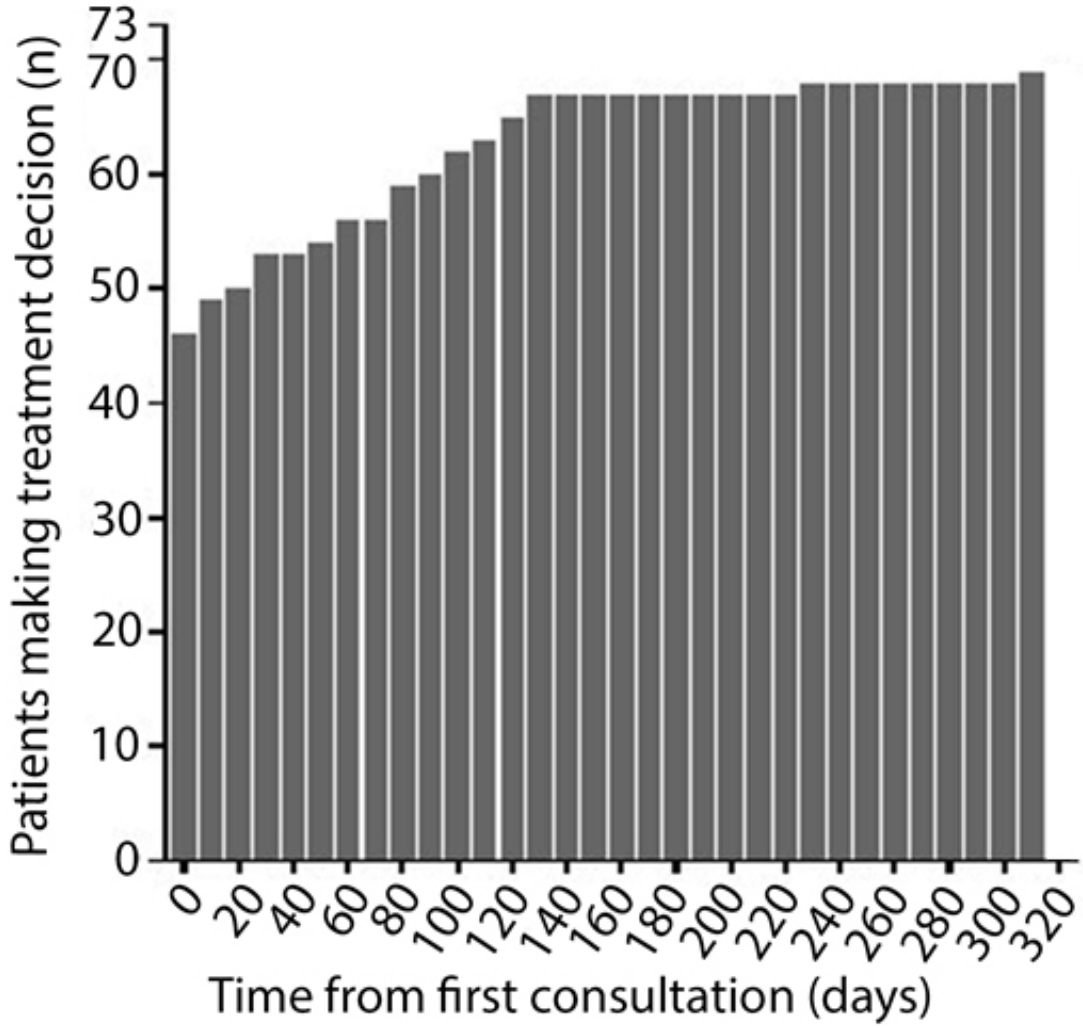

Figure 14: 'Treatment decision 'followed through' as measured by time of consultation'

Decisions made after the consultation result in treatment initiation, improved treatment satisfaction and reduced DC

After one year, DC was reassessed to determine if it had changed. Forty of 73 (55%) responded of which 37 were usable and these responses were compared as the future group (n=10) to the past/baseline group (n=27). Three measures of DC were originally used (SURE scale, SURE sub-scale and DCG) but by assessing change in DC, it was not possible to use the SURE sub-scale measure here. Using the SURE scale 6/10 (60%) of the future group reported their DC resolving compared to 3/24 (13%) of the past/baseline group (Fisher's p=0.008).

Furthermore, the DCG scale also demonstrated a significant improvement, with 8/10 (80%) of the future group reporting a decrease in DC, with the remainder staying the same compared to 9/27 (33%) of the past/baseline group improving, 4/27 (15%) staying the same and 14/27 (52%) showing an increase in DC (p=0.01). Supporting that this was related to starting treatment, 9/10 (90%) in the future group changed from dissatisfied at baseline to satisfied with their treatment status at year 1 compared to 6/27 (26%) in the baseline/past group (Fisher's Exact Test 2-sided p=0.000).

3.20 Results - Interviews

Interviews reveal many practical issues potentially producing DC

To gain more insight into social factors that may influence DC and why treatment status is affected, pwMS from the 'offered treatment' cohort were approached for interview. The interviews (n=8 with seven individuals, included two interviews with the same individual (subject 001) a year apart) revealed confusion and frustration particularly with the treatment pathway. The demographics of the interviewees are shown in Table 9 and compared to the overall cohort. An overview of the interview findings are provided in Table 10.

Table 9: Demographics of total MS-DOUBT cohort and comparison to MS-DOUBT sub-cohort (interviewees)

Parameter	**n, %, missing**						
	'Offered treatment' (n=73)			**Interviewees sub-group taken from 'offered treatment' group (n=7).**			**P-value (comparing cohorts)**
Relapsing MS	68, 94%, 1			7, 100%			NS
MS diagnosis (0-3yrs)	32, 46%, 4			2, 29%)			NS
Treatment naïve	22, 31%, 3			1, 14%			NS
Treatment potency (no treatment (0), moderate (1), high (2))* number on [injectable/orals]	0=39, 53%	1=30, 41% [7, 22]	2=4, 6%	0=3, 43%	1=1, 14% (oral)	2=3 43%	NS
Male sex	17, 23%			2, 29%)			NS
Age 18-44 years	40, 55%			3, 43%			NS

White ethnicity	59, 82%, 1	7, 100%	NS
With partner**	33, 52%, 10	7, 100%	0.03
Employed	45, 68%, 7	6, 86%	NS

*The moderate and high potency treatment groups were compared. No significant difference was observed between the moderate potency groups but there was a difference when the high potency groups were compared (p=0.01, 2x2 Fisher's Exact Test).

**It was unclear from the original paperwork if two participants had partners but this was confirmed at interview. This was the only significant difference observed in demographics (p=0.03).

NS – not significant

Table 10: Key themes emerging from interviews factoring treatment history, status, priorities and response to diagnosis.
Individual characteristics are not included to protect the identity of participants. Each subject has been allocated a random code and colour so comments across themes can be associated to the same individual. Average duration of the interviews = 1 hour 45 mins (range: 54 – 266 mins).

	Subject number and associated colour						
	001	**005**	**010**	**024**	**029**	**037**	**040**
	Blue	**Orange**	**Red**	**Green**	**Purple**	**Pink**	**Black**
Themes	**Subthemes**		**Codes**		**Example statements (subject number)**		
Issues with healthcare system	Communication (Negative)		Lacking Advice/support of HCPs; Not knowing what appointments are for; bad experience at diagnosis		"[On diagnosis] The neurologist's bedside manner was not particularly outstanding. He told me I was primary progressive, I did not know what primary progressive was. I knew what MS was - loosely… There was no talk about medications, treatments or anything. It was very short, very perfunctory and I walked out of there thinking what do I do now?." (001) "[On neurologist's delivery of diagnosis] "He blurted out I wasn't prepared: 'I think this is MS' and that was how I was told and it was just a bolt from the blue…very blunt." (005). "That first appointment I went to see [nurse] was horrific. [Partner] came to see me and we sat there and she asked if I minded that this other lady was there – I can't remember – and it was like I was a laughing stock. I remember sitting there and her saying 'and one person has died but don't worry'. I was taken aback and they were just joking. I had questions that I asked and they couldn't answer the questions and they were not sure and this and that… I just stopped asking questions, shut down and didn't want to discuss it any more." (024). "I was so cross when I went to Birmingham and this doctor sort of said to me 'oh you don't look that bad to me and I certainly wouldn't prescribe that medication and that's quite nasty and have you read up on the side effects?' and I said 'yeah I have but I don't want to live like this either…Everything is down to MS. I've changed my GP because the first one		

			was just a nightmare. You know, the first visit that I ever had she said: 'well you're a patient with an acute and chronic life-long condition that is completely under-treated, what do you want me to do?'." (029) "I had a very bad experience with the doctors….he said you are secondary progressive and there is nothing for you – I can't believe this is true when I consider I am young." (037).
	Communication (Positive)	Patient's decision to make; don't rush; additional support from nurse	[Neurologist] was very good. Very busy but when he did see me he was very good." (005). "[Neurologist] was very good the first time I saw him and he prepared me for what type of medication and the options that were available to me. He said not to make a rushed decision. He said that some people get the diagnosis and I don't see them again and they just disappear, but he was very much on the fence and it was my decision to research and what he suggested was to go and see an MS nurse …to talk about the condition." …"I was referred to an MS nurse. It's a pain to go there as it's so far away but he was amazing. He was the only person who actually explained things. He gave me his e-mail address and everything – [MS nurse name removed]. Five minutes after talking to him [MS nurse name removed] I burst into tears and he was like 'what?' but in five minutes he explained everything to me after months of frustration. He said we have all the time in the world and he e-mailed me. He was just so good – other people I spoke to, even doctors, they just sat on the fence, where as he said: 'if you have an option of winning a lottery ticket and we give you the numbers would you take it?' and to put it into that perspective, there are lots of benefits – potentially – lots of benefits so it made sense to start earlier rather than leave it [treatment]." (024)
	Systemic issues (Negative)	Postcode lottery; slipping through the net; lost in the	"I'm getting a bit sort of anxious and upset now because I think I've slipped through the net somehow…I rang up the number that [the nurse] gave me and they

		system; cause of anxiety	didn't have any trace of me whatsoever [at the hospital]." (010) "I don't like the fact that it depends where you live, because [county name removed] has a poor reputation for diagnosing." (040).
	Systemic issues (Positive)	Clinical trials meant closer monitoring	"[On clinical trials] Marvellous, and that's another reason I did it because of the monitoring where you're in a system that provides support – as much support as can be provided." (001).
Treatment issues	Proactive approach	Doing trials; chasing appointments at hospital	"You have to put yourself out there, you can't just curl up in a ball." (001)
	Education	Online resources; staged approach to learning; family assistance; need assistance beyond information booklets	"My dad was really amazing…the moment MS passed out of my mouth he did a lot of research for me. He filtered. I was told careful where you look because you're going to scare yourself…so I kind of left it to my dad." (005). "I go online where I've got printers at work and I look everything up and then I print it all off and then I bring it all home and then I read it and then I put it away and then I re-read it again." (010). "You're given a booklet and [told] read the information about this medication... You need someone to go through it and look at it." (024).
	Treatment history (experience)	No quality of life; side effects; Drug administration; drug frequency; positive experience, decisional regret	"Because I'd had a bad time with Rebif every other day injecting and the fact that this was once a year as opposed to Tysabri which was every month, this kind of made sense to us [referencing partner]….I liked [Rebif] because it was home administered; even though it was more often, it was convenient. In hindsight I might not have chosen Rebif because of the bigger picture – it was restricting because it was refrigerated and it became clear I couldn't go too far away…travelling and getting about,in hindsight I would have gone for Tysabri. Having it once a month and getting it over and done with. I regretted it

			because my body became sensitive to it." (005). "[Rebif] made me unwell…Copaxone…I was on that for seven years. I did quite well on that. Tysabri was the best thing I was ever on. I didn't think I had MS at all – I was brilliant on it. So I was devastated last year when it all went wrong. I really was….Every treatment I have been on has been a big decision." (010). "I quite like the idea of not having to take something every day… taking medication every day reminds me that I'm sick and I don't want to be sick. Whereas if I'm having a one-off treatment and even if I'm having blood tests, that's a lot better than having tablets. And I think tablets can cause you longer-term problems. They can upset your tummy and all of that kind of malarkey." (029).
	Asymptomatic	Don't want to disrupt equilibrium; could it be more dangerous to take treatment	"[Following diagnosis] I walked out of there and thought that is that then. I remember thinking there is nothing wrong with me… so for him [the neurologist] to say to me we need to get you on to whatever form of treatment regime I would have said why?.'' (001). "You are taking medication that I might not need – why put my body through this?." (024). "At the moment because I don't need treatment for MS, having treatment for MS, I would want to know that it is going to have a good effect. I don't want to be given treatment for the sake of it…I've got this idea that if I did take something, it won't worsen it, but it won't help it either. It is the after effects that bothers me, rather like the shock of falling, will it trigger more MS? I have heard of this. If the treatment is too aggressive and it's kind of solving one area of MS, is it upsetting the quiet benign, unknown areas of MS that haven't yet said hello?." (040).

	Lack of knowledge	Confusion	"I have this condition and I don't know anything about it. I don't know where to get those answers from. I was told to go to the MS Society and if anybody else has MS and if I could talk to somebody. I never felt confident doing that. So it's kind of like you are told and then it's up to you to find out information." (024). "I am still amazed after all these years of sometimes worrying about my health that I actually got something that was not on my radar [MS] but we can cope with it. I don't research terribly much about it….I don't know what the main medication for MS does. For me there should only be one that stops the myelin sheath wearing out. Apparently there are many. I do know that some of them work in some respects but some people don't take them because it makes them feel funny. It's very naïve. I haven't researched them, I don't need them yet, I may not need them at all." (040).
	Treatment works (efficacy)	Feeling better; symptoms; symptom priorities	"I was totally confident with [treatment] Tysabri, [it] was never an issue… At the beginning I gave some thought to the JC virus but not beyond that." (001). "I would like to walk a bit better because the walking has a very big effect on my illness." (037).
	Interpreting risk	Risk viewed as a potential; hopeful not life-threatening; weighing up benefits and risks; being aware of significant risks of more efficacious treatment	"Anything that is bad that can happen is on a massive list of potentials [referencing treatment] and would be monitored so the hope was that it wouldn't get to the point it was life threatening…. [Re: treatment Lemtrada] the issues for me were around the benefits weighed up against the side effects, of which they were more significant than any other drug I've come across before. All of them were quite heavy." (001).
	Partner influence	Supportive; helps inform treatment decision	"I talk to my husband about it [treatment]. I mean we've been married an awfully long time so he knows me more than anyone else. And he will always say I will back whatever it is that you want to do but

			at the end of the day it's your decision." (010). "Both my partner and myself wanted to decide to tackle it hard [MS]... what's the best [treatment] out there at stopping or reducing relapses." (005). "[On stem cells] my husband read a lot about it." (037).
Perception of MS	Stigma	Caring what others think	"[On MS diagnosis] I never volunteer the information to anyone, ever." (010). "It's like a label that I am really ashamed of and no-one knows." (024). "[On MS diagnosis] I would like to say but I don't think society is ready." (037).
	Ignorance	Stigma; lack of knowledge; caring about what others think; should be one treatment not many	"People look at me and think 'well you look alright to me'. And that's another thing isn't it, because not all disabilities are visible disabilities." (029). "People have said things like 'oh my uncle had MS and he died from it'…I am surprised at people; the tactlessness… She said her daughter has MS. I said I had been diagnosed. He said 'yeah she's been given six months'. I looked at him and I looked [at his wife named]. I left the room and had to lie down. I was more furious than shocked. I nearly flew at him: 'There is no such thing as a six-month diagnosis, having had MS diagnosed– that's not how it works mate." (040).
	Threat to identity	Maintaining mobility; sense of pride; career influence; vulnerability; male identity; MS should not define me; switching of roles	"Mobility is crucial to me from personal pride and dignity...It's absolutely a pride thing because the career I had involved mending people's broken lives, if you like, and it's very difficult to let that go and it's the vulnerability that MS gives you and I don't want to accept vulnerability. A lot of it is probably a male thing but I won't let that happen. It's very hard to let that go. We all have to get old and one day it might. It's probably a male thing, but I

			don't want MS to define me. That would be the worst possible thing.'' (001). "I've always been the carer not the recipient. And I don't like the role change. And I don't like to think there is that lack of control. And it doesn't help when they take the mickey out of you when you're in your wheelchair and they say they're going to let go down a hill because they think it's funny. I know they wouldn't do it but they always threaten to do it. You know, because they think it's funny. [the wheelchair] It makes me look disabled. It's the way people speak to you as well, you know - because you have full cognitive function." (029).
	Fear of progression	Fear attributed to observing disability in others; how it is perceived by others; the unknown; managing expectations; being made fun of	"I joined a therapy group…the first thing that hit was me was people sitting in motorised vehicles. That was a psychological thing.'' (001). "I was thinking wheelchairs, early death." (005). "I worry that I will be disabled and that I can't walk and that I can't move when I'm older." (024). "I don't want to become disabled. I'm really, really scared of that." (029).
	Denial	Psychological impact; Non-acceptance; Ignoring MS	"I think part of my psychological thing is that I haven't accepted it [the MS] and I would be the first one to say that you haven't accepted your own illness so how do you expect others to?." (029). "I've went through the thought process of 'live today, don't worry about tomorrow." (040).
	Giving back	Involved in trials; Holistic attitude	"MS didn't dominate my life in the way it has in the last six months, so in that sense I thought it important to go on to trials from the point of view of the holistic attitude." (001).

	Positive side to MS	Taking part in adapted sport; social element; encourages independence; MS interpreted positively	"I joined [name deleted] rowing club, they have the first or one of the first adapted rowing sections in the country and I was introduced to that through a guy I train with. I go there every Friday morning for 2-3 hours and you're coached and the boats are equipped. They're hard to stay up in full stop, as you can imagine, if you have no balance. You take part in regattas. A lot of it is psychological and it gives you that independence and it makes you realise you can still do things and to be honest, I wouldn't have done a lot of these things without the MS. There is a very positive side to it too." (001). "I care more about people and people's needs." (037).
Miscellaneous	Partner influence (Negative)	Husband useless; Anger and frustration; not being able to relate to MS; feeling ignored	"My husband is useless. I love him most of the time but he has absolutely no idea about any of this and to him the only way of coping with it is to pretend it's not happening. And if I'm having a very bad relapse when I'm really tired, he just ignores me. He's actually quite nasty because he can't cope with this illness." (029)
	Work	Being late for work due to fatigue; falling at work; adapting at work; fear of losing job	"The hardest thing for me was, with MS, having to come in off the street for the last four years and work in an office" (001). "I kept being late for work because I was just so tired. Which wasn't – isn't – me at all…I've had two really bad falls at work where I've injured myself falling over….I don't want to give up work yet but if I keep having relapses and taking time off work, are they going to say to me, it's time you retired? Is it time you stopped? I don't want anyone to say this to me yet." (010). [Said to neurologist concerning work and the MS diagnosis] "this is very confidential and I don't want anyone to know... Only my partner and friend knows – two people." (024). "I've chosen to work mornings. After the last time I got absolutely whacked out and I was miserable and tearful and all the rest

			of it…I was working four days then, and I thought, I just can't do this. I just can't do it. So eventually, after a change of personnel work agreed, that they would consider allowing me to work mornings… So I work quarter to nine until quarter to two with a twenty minute break." (029).
	Recognising own limits	Planning ahead; knowing own limitations; acceptance	"In my head it's the MS. I can only walk a certain distance these days. Do I want to go up the stairs three times in a morning? Can I manage going back upstairs and coming back once? Yeah probably, but it's facilitating the start of the day." (001). "My husband is going to [horse racing, name removed] next Tuesday…I used to go with him, but I know now I can't. Because I can't walk around there all day – things like that you know. So you are more conscious of what you can and can't [do]… A good day is being able to get up at say a normal time, say 7 in the morning and not having to sleep during the day and actually have enough energy to do what I've got to do. I find that I can't do any more. I can't do what I used to be able to do but I can usually do what I've got to do providing [daughter's name] does the majority of cooking in the evening." (029).

Three main themes emerged from the initial coding and sub-themes which are addressed in order here. There was an additional miscellaneous category which referenced for example, work. This did not merit a standalone theme, nor did it fit into the existing three categories but is included here for completeness.

3.21 Discussion – qualitative research (Interview themes)

3.21.1 Issues with the healthcare system

3.21.1.1 Communication

There were many issues discussed that could be associated back to issues within the healthcare system as a main theme. Although there were some positive comments, the challenges within the healthcare system had greater prominence. Some of these challenges included the poor delivery of information and how it was delivered by the HCP; not knowing what appointments were for; delays and having to chase HCPs for answers to questions.

There were negative memories surrounding diagnosis and the way it was delivered. Some of the sub-themes included misdiagnosis and communication of diagnosis. The delivery of other HCPs such as nurses and GPs were questioned. They were perceived as lacking tact or knowledge about MS.

However, more successful clinical encounters were also recorded. Sub-themes within this included feeling listened to adequate explanation of treatment options available. To be given a contact number and a 'go-to' person in case of issues was well received.

3.21.1.2 Systemic issues

At a local level, problems with appointments and not knowing what they were for as well as problems with access to the healthcare system came up regularly. On a broader level, where a person lived was referenced as relevant to accessing MS services and what could be prescribed i.e. a 'postcode lottery'.

3.21.2 Treatment issues

From a positive/neutral perspective, participating in clinical trials was perceived as a worthwhile experience pertaining to the additional care and attention; being proactive concerning the condition and seeking out the latest treatments, as well as a sense of 'giving back' through research participation.

When it came to treatment approach, there was a sense that the HCP was very much leading on the decision-making in terms of presenting treatment choices and a feeling of expectation that it should be led from this end by the HCPs. This may have been exacerbated by experiences of being taken off treatment due to side effects or other risk factors – which could also unsettle the patient, especially if they felt it was working for them. One patient was taken off natalizumab as part of a clinical trial when the trial outcome was not met, whilst another was taken off the same drug at short notice due to safety concerns. However, both felt the treatment had been working for them.

Generally, treatment was favoured by the majority.

In terms of treatment knowledge, again there was a sense that this should be offered by the HCP. However, there was additional research carried out by some of the patients but this varied per individual. One patient remarked that they would weigh up the risks and benefits of the treatments available whilst another would absorb information in stages, over time, by returning to information that they had printed about a treatment. Partners were also mentioned as influential as part of the treatment decision-making process, consistent with the findings in chapter 2.

3.21.3 Perception of MS

Coding revealed an acute awareness of what pwMS felt others were thinking about them as well as the impact their condition had on others. The participants were aware of their impact on others as much as the impact of the disease on themselves. An example was questioning of a daughter's role in helping her father:

> *"I remember falling over... people stepping over me because they thought I was a scuzzy old drunk and that was demeaning… My daughter was with me and she went off to the shops. I remember having a cane, having to hold on to my daughter's arm. Stability is the issue. But bearing in mind she was 15 at the time, it's not fair on a kid to have dad hanging off her arm."*

Within the quote above and elsewhere within the transcriptions, there were clues as to the reversal of roles that people observe e.g. parental into child and from carer to recipient. Identity itself was therefore being evoked in the individual, which could be attributed to how they perceived MS. This could manifest as a personal role within a household, but also a work-related role now diminished (due to adaptions or reduction of working hours).

Work and the status and security it can bring have been aligned with a person's sense of self which is not surprising when it occupies a large portion of adult life (Gini, 1998). Research has differentiated perception by treatment and disease (de Seze et al., 2012) and the findings here consistently point towards perception of the *disease* over treatment. This could be interpreted as fear of the future coming from observing MS in others at a more advanced stage of the disease.

3.22 Discussion – Quantitative research

The clinical encounter contributes to resolving DC and in turn is impacted by satisfaction with the HCP. When factored among other drivers to the clinical encounter, PAM is the main driver of DC. However, when SDM is factored, it also plays a role and is consistent with previous research (Politi et al, 2013). This builds upon earlier work, looking at a cross-sectional population of pwMS, which showed that DC was associated with less satisfaction with treatment, being of non-white ethnicity, being in employment and on a less potent treatment and was highest in those attending a conference to find out more about therapies available (Wilkie et al. 2019).

In complex decision–making, a well-managed clinical encounter with mutually agreed outcomes - as supported by SDM - is associated with less DC in the future, indicating that a 'good' decision has been made. In those faced with a complex decision about their MS therapy, dissatisfaction with treatment or not being on it as well as having less confidence in healthcare decision-making is associated with DC.

In this context, the face-to-face consultation and optimal SDM appears pivotal to improving outcome in terms of DC, with high levels of SDM being associated with lower DC. By studying when the group made their decision as opposed to actually starting treatment, it was found that most of the group made their decision prior to or in the consultation with 19/73 (26%) making their decision afterwards with 3/73 (4%) not deciding by a year when followed up. At one year, in those who decided after the consultation, there was improvements in DC and treatment satisfaction.

A range of instruments were used to map the three stages of decisional process of those deciding about DMTs in MS, with the aim of gaining more insight into how they interact at each stage and impact DC. A key aim here was to understand if DC, as an outcome, was impacted by the consultation and whether DC could be used as a basis in the future to inform the consultation process. The approach used derived from prior work where the failure of a decision aid in diabetes was attributed to missing the doctor/patient interaction (Hargraves and Montori, 2014). Here DC was attributed to the DMT decision by framing this within the question (Wilkie et al., 2019) but also three measures were used, two of which were independent measures of DC, to give further certainty of any findings.

There are often delays commencing DMTs, thus there was follow-up if and when the decision to start DMTs was made - by checking with the patient and their medical records. When reassessed a year later, again DC was related directly to DMT decision though much may have occurred in the timeframe. For this reason, multiple DC measures were used to verify the results, with further support of a link to starting DMTs arising from the fact that the group also had significant improvements in treatment status.

The first stage of decision-making, the prerequisites, are features a patient brings to the consultation. Of the prerequisites, engagement, as measured using the PAM score, is the only consistent feature associated with DC as measured using three different measures. PAM is known to have a real world impact with people who recognise the

role of managing their own condition experiencing better healthcare outcomes (Deeny et al., 2018).

For the consultation, it was found that overall the patient had high levels of confidence in the HCP with some HCPs preferred as seen previously (Roberts et al., 2014). During the clinical encounter, the patients' most valued points of discussion were 'Asking about your symptoms', 'Listening to you', 'Treating you with care & concern' and 'Taking your problems seriously' (Adjusted R^2 .316, p=0.000) (Croker et al., 2013). Bearing in mind that the consultation principally was about starting therapy, it is interesting that 'explaining tests and treatments' and 'involving you in decisions about your care' were not significant to patients. This may be giving a hint as to what is valued by the patient versus the HCPs' perception of what should be discussed. Reinforcing the importance of this discussion, a good clinical encounter is associated with higher levels of SDM and in turn a high level of SDM perceived by the patient was associated with lower DC. However, again there is evidence of differing perceptions of the consultation, with HCPs' perception of SDM during the consultation being consistently higher than the patient equivalent.

Seventy per cent of patients had already made their decision or made it during the baseline meeting. In this group, there was a trend to higher PAM scores and less DC, but the fact that they had made their decision may explain why they were not as concerned about the 'explaining tests and treatments' element of the consultation. In 30%, the decision or not occurred after the meeting and a novel part to this study was that the medical notes were reviewed and patients were followed up to a year later to

ascertain when the decision was made. This allowed the decision to be followed over time and, indeed, the treatment intention was recorded as a mean of 29 days later (range 0-308 days). The thesis author could not find published data on how long it takes to decide regarding DMTs and 4% had not made a decision by one year. Though only 55% of patients completed the later assessment of those who had made a decision, there was improvement in all DC measures and in treatment satisfaction - thus supporting that a successful decision is related to starting treatment.

This work offers insight into the process of complex decision-making where multiple HCPs may be involved in the process, but other information sources such as the internet have an increasing influence (Powell et al., 2003). Indeed, patients come to the meeting with a decision made or that they are ready to make a decision. However, despite this, this work reiterates the status of the clinical encounter (Edwards and Elwyn, 2006) and guides us as to what elements of the consultation are valued; furthermore, it has been demonstrated how SDM is a vital element for patients. Finally, DC is a useful outcome in this context with the potential to assess the 'success' of a clinical encounter. This is important as an area has been pinpointed where HCPs may need to focus to get better outcomes from the consultation.

Here an attempt has been made to map the instruments across the decisional process with the aim of gaining more insight into how they interact at each stage. As figures 10 and 11 illustrates, people bring their own beliefs and circumstances to the consultation (prerequisites) and then the consultation is an opportunity to address these in the context of starting, changing, delaying or ending treatment. DC interacts with

this process depending on the individual, and is a method for assessing the success or failure of a decision as an outcome measure in this context.

When the consultation was isolated, the results suggested that the conversation with the HCP may resolve much of DC. This work aligns with previous research which suggests it is the involvement that benefits patients, not the action of making the decision and perceiving who makes it: doctor or patient or both (Edwards et al., 2006).

Among the drivers that people bring to the consultation, PAM had the most impact. PAM is an indicator of a person's confidence and readiness to make a healthcare decision so it is not surprising that there is a connection to DC. Married to the components that have already been seen to drive DC, PAM is a measurement that could be used to gauge the approach the HCP should engage the patient about treatment options. That said, whilst many clinicians may recognise the importance of SDM, how patient involvement is carried out is not clearly defined (Politi et al., 2013). Any approach is complicated by a person's own values and role preference, as measured here by the CPS, which indicates the majority of the cohort prefer an active-collaborative role in their treatment decision-making. This contrasts with a German study where the majority preferred an active role (Heesen et al., 2004) and an Italian study where the majority preferred a collaborative approach (Giordano et al., 2008).

Self-management in long-term conditions such as MS has been highlighted as important. Those who effectively manage their own condition with the appropriate skills and know-how to apply them, experience better health outcomes (Hibbard and Greene, 2013). In terms of magnitude of change, a single point increase on the raw

score of PAM has been correlated to an increase in treatment adherence and a decrease in hospitalisation (both 2%) (Insignia, 2015). In diabetes patients, a ten point gain was associated with a 17% decrease in the likelihood of requiring hospitalisation (Remmers et al., 2009). There are approximately 12 points between levels across a 100 point continuum and a one point increase is important (Gross, 2017).

There is real-world impact with those who display the highest PAM levels. Previous research has attributed those at the highest level with:

- '38% fewer emergency admissions;
- 32% fewer A&E attendances;
- 18% fewer general practice appointments; and were
- 32% less likely to attend A&E with a minor condition that could be better treated elsewhere' (Deeny et al., 2018).

Therefore, establishing the PAM levels of existing patients could be crucial in identifying priority needs in those individuals.

In terms of patient knowledge, a poor understanding of risk was observed. As risk has been linked to making an informed decision (Heesen et al, 2017), it is pivotal in the decision process, especially as the spectrum of treatments in MS increases year upon year. How this information is presented and best interpreted is a further issue for HCPs and patients. Feedback on the RIKNO questionnaire was that it was challenging, whereas the MSKQ was more accessible. Such is the nature of the changing treatment

options available in MS, as well as the risk knowledge evaluating them, the questionnaires require updates over time, and they are perhaps not suited to longitudinal studies for this reason. The MSKQ also required adapting to a UK audience – for e.g. a question on the prominence of MS and by gender varies by territory. However, as a general indicator of knowledge across a population, both the MSKQ and RIKNO can be useful tools. This study was consistent with previous work, which saw less than 50% of questions on RIKNO (version 2.0) answered correctly (mean 8.9) compared to 80.4% in the MSKQ (mean 20.1) (Heesen et al., 2017).

In a study by Heesen et al (2010) comparing patients' with physicians' risk perception of treatment with natalizumab, patients were more accepting of PML risks compared to neurologists (Heesen et al., 2010). As risk knowledge may help determine treatment choice, it is essential that numeracy and literacy skills of patients are calculable so they have the ability to absorb such information, or that information is presented in a way that is simple and accurate enough so as not to discriminate and to encourage health equality.

There are considerations when using the TEIQue in order to inform future researchers, especially in an MS context. Results of the TEIQue were shared with the interview participants and the feedback was generally positive and consistent with participants' own perception of their personality and behavioural traits. Across the total population only adaptability came out as different to the general population (a borderline result). The data was independently converted as per the licensing agreement and although raw values would have been preferable and were ultimately

made available, interpreting these comes with additional cost. The TEIQue also required training to administer and interpretation of the raw scores so subtleties in the raw data were potentially missed. Several questionnaires came back incomplete due to the volume of questions (153 items) and clarity was sometimes required as to the meaning of questions from patients for e.g. what does "ordinary" mean in the sentence 'I am an ordinary person'. This was evident by the lower number of questionnaires completed (n=55) versus some of the other, shorter measures (see table 8).

This study has some further limitations. The SDM-recorded outcome is helpful in capturing a direction of approach at the end of one consultation, but limited by the constraints of that consultation; for example, a person may not be able to decide on treatment by the end of one consultation because they require further review and investigations. There is therefore a lot of malleability within one decision and a fuller picture can only be obtained by accessing the patient's clinical notes: in other words, the consultation elicits a treatment decision but the final decision is not necessarily made inside the room and the process itself must be pieced together. Decisions are also influenced by external factors unique to the individual as the interviews showed.

In addition, there are a number of health-related outcome measures e.g. treatment adherence and use of self-management services, that have not been included here, particularly with reference to the PAM measure, which has seen an impact on adherence in chronic conditions. Finally, the SURE instrument produces a binary result when DC is a process.

3.22.1 Interviews

The interviews revealed gaps in the healthcare system highlighting two areas within the healthcare system: HCPs and problems with the system itself. To a degree, the problems within the system itself can be relayed back to the HCP as it is the HCP who essentially delivers the system in which they operate, although there will always be macro-level processes that must be followed and that can't be solved at an individual level.

In terms of overcoming these issues, more training could be given to GPs and other HCPs who may underestimate the impact of the information they communicate and how they communicate it. Again, problems within the healthcare system e.g. not knowing what appointments are for, could be solved with explicit communication as to the plan of action, why and when. For example, the clinical trial experience was considered positive in view of the greater attention the patient often receives relative to the standard patient pathway.

Another indication of a positive experience is how time is used by the HCP. One HCP received more positive feedback versus colleagues, but there was nothing to indicate that they spent more actual time with the patient. This suggests that a sense of time can be communicated rather than experienced and may be aligned to the HCP's own experience and personality. Allowing the patient to feel they have sufficient time to make a decision is important and is consistent with previous research looking at patient priorities (Oreja-Guevara et al., 2019).

3.23 Conclusion

In the next chapter, the findings from the MS-DOUBT study inform the creation of an intervention in the form of a film with the aim of engaging patients in the treatment decision-making process.

3.24 Acknowledgements

The thesis author would like to acknowledge the HCPs and most importantly the patient population involved in the research who gifted their opinion and time to the study.

3.25 Contribution to work

David Wilkie: Wrote the study protocol and patient documents and obtained all regulatory permissions (ethical and internal and for licensed measurements). Approached all participants and obtained consent and followed up with participants as appropriate. The thesis author entered all data and performed statistical analysis and adaption of figures and generating of tables (with the exception of those attributed to Richard Nicholas); organised and performed the interviews and subsequent transcribing and analysis. The thesis author was also responsible for writing the content published as introduction, methods, results, statistical analysis and conclusions sections within the published paper.

Richard Nicholas: Advice throughout project; selection of patients; responsible for original figure 13.

Alessandra Solari: Proofreading the manuscript; advice on sample size; advised to split population by DC (table 6).

Joe Hill, Michelle Brownlee, Leilani Cabreros & Eleonora Rigoni: For permission to use their image for figure 10. All are work colleagues of the thesis author.

3.26 Conflicts of interest

A Solari was board member of Merck Serono and Novartis, and received speaker honoraria from Almirall, Excemed, Genzyme, Merck Serono and Teva. R Nicholas is funded by the Imperial Biomedical Research Centre (BRC) and R Nicholas and D Wilkie are funded by Multiple Sclerosis Trials Collaboration (MSTC).

Chapter 4 MS-Film study: evaluation of a decisional tool

4.1 Introduction

This chapter aims to address the following research questions that have emerged from the previous chapters:

- PwMS feel disengaged from healthcare decision-making
  - how do we increase engagement?
- People absorb healthcare information differently
  - can information be communicated in a novel way?
- DC and DR increase in treatment naïve pwMS
  - can this group be targeted?
- There can be resistance to action following diagnosis or/and treatment decisions - how can healthcare information best be delivered?
- Some people are outside of the healthcare system
  - how do we access them?

In addition to the above issues, there is evidence that:

- Early treatment intervention can improve medium-term prognosis in pwMS
- Treatment is associated with lowering DC and DR

In response, a decisional tool was proposed to educate pwMS about the consequences of delaying action and the importance of early treatment intervention in MS. In contrast, a DA has been defined as a tool that presents options and their features to a

person, as well as facts about the condition or disease being presented. They assist in identifying what is important to the person in terms of their values and to deliberate these with an HCP (Stacey et al., 2014). Based on this, the film presented here does not fulfil this criteria and therefore another classification is necessary. For this purpose, a decisional tool is proposed here, which presents information that is implied (in this case through analogy), and used on the basis that the participant are primed to supplement their understanding with further investigation. Here investigation is measured by applying the film's concepts to the questions on self-perceived understanding, which is necessary by visiting and reviewing the website in addition to watching the film. The film therefore can't fulfil a DA's criteria in its standalone form. The film has the potential to be presented as a DA, if it was to be used alongside the presentation of alternative options for comparison (e.g. a second film presenting explicitly the results of taking action or comparison with routine care pathways), as well as the opportunity to discuss the film's content with an HCP (e.g. through an RCT).

The creation of a decisional tool was therefore achieved through film narrative, the rationale for which had its origins in behavioural science, and specifically nudge theory.

4.1.1 Behavioural science

'Nudging' is an established but evolving aspect of behavioural science (Thaler, 2008). The idea of 'nudges' are small, often imperceptible changes to choice 'architectures' that are intended to exert a positive influence on people's choices. However, whilst some nudging has been described as emphasising shame to the person, e.g. smoking (Voigt, 2014), the approach here was to use nudging to encourage people to make good decisions, but not to force them to a specific decision. The film therefore does not tell people what to pick from a range of treatments, but highlights instead that they should be a consideration.

Nudging has been taken seriously enough to merit a government body in The Behavioural Insights Team (BIT) (BIT, 2018). Thaler (2015) explains the origins of BIT having been approached by the Conservative party in 2008 (ahead of a coaltion government in which it was implemented in 2010), with the aim to use behavioural economics and science to make government efficient. It was proposed that this could manifest as new policy. There were two broader aims: firstly, to spread behavioural change across government and furthermore to achieve a ten-fold return on the so-called 'Nudge unit's' costs (Thaler, 2015), (Wikipedia, 2020a).

Real world examples of behavioural change in the U.K includes a small tweak to wording sent to patients – to include the £160 cost of the appointment – resulting in a reduction to non-attenders to NHS clinics by almost a quarter (Darzi, 2015). Another application of nudging has been seen as part of smoking campaigns, placing photographs of diseased arteries on to cigarette packets to alert people to the dangers

(Hunt, 2016). Over time, the intention is to make the products less attractive to consumers (Guinard, 2014).

One rationale for using this approach is the belief that people can be inconsistent by nature with short attention spans. That people put off important decisions and prioritise in the moment satisfaction and, with it, dismiss the rewards of the future (Reeves, 2008). Ultimately society benefits usually in the form of savings. In the context of MS, people who start treatment early have a better prognosis and this not only benefits the individual but society at large, for people can remain in work for longer and the healthcare system is not as pressured if pwMS are living healthier, mobile and productive lives without disability.

The film builds upon the guidance of Pawson and Tilley (1997), engaging the user to think about their situation (Pawson and Tilley, 1997). In this instance, the situation being scrutinised is of non-action or feeling disengaged. In addition, the film utilises and adapts existing academic theory to inform its causal assumptions; its creation is based on 'real world' experience having been informed by previous research engaging three populations of pwMS acknowledging varying needs. Some of these needs have highlighted that not everyone is engaged in the same way despite (or because of) a range of treatment options and the reality that people are at different stages of the decision-making process. Therefore one approach does not suit all. The fact that a number of films already exist on MS and yet, there is a high proportion of people with DC, indicates that creativity is needed when it comes to presenting healthcare information.

4.1.2 Existing interventions in MS

A number of DA exist in MS with the aim of supporting or presenting treatment options. Those with RCT application have been summarised in chapter 1 and appendix A.

The existing DA used in MS and described in subchapter 1.13.2, are primarily paper-based and involve a substantial amount of time to review. A scoping review of video-based patient DA published in 2018, could find only five in the neurology field (2009-2015) and none aimed at MS (Winston et al., 2018). Elsewhere, the lack of RCTs investigating the direct impact of film on public health has been highlighted (Botchway et al., 2017).

Available online, there are many films around the subject of MS that are a mixture of personal accounts from those living with the condition (MS_Trust, 2017), pharma-endorsed productions that show the mechanism of drugs currently available or/and the latest treatment approaches (Biogen, 2016), expert interviews (UCLH NHS Trust, 2016) and presentations (Holland Hospital, 2013), symptom-specific films that address for e.g. fatigue (Thrower, 2015) to diet (National MS Society, 2016a) and exercise (National MS Society, 2016b) as well as films exploring the causes of MS and presenting it in a scientific way with graphics and animation (Ali Feili, 2015).

The idea behind the film proposed here was not to 'reinvent the wheel' but instead, to employ a different approach whereby the film is not a classic decisional intervention as defined by the Cochrane Collaboration or IPDAS criteria (introduced in chapter 1). This was confirmed by expert colleagues at a decision-making event in Germany, held

in 2018. Hence the IPDAS criteria has not been followed for this reason. The film is more closely aligned to a healthcare application of nudge theory and will be referred to henceforth as a 'decisional tool' or 'film' interchangeably.

A small group of participants were informally interviewed from the 'offered treatment' cohort informing psychosocial variables for the theory of change model (see Figure 15) underpinning the film's rationale. These were patients who had consented to the MS-DOUBT study whom the thesis author encountered in outpatient clinics. As stated, the conversations were informal and for this reason the demographics were not recorded. In addition, the MS-DOUBT subcohort of interviewees had stated their frustrations with the healthcare system, issues around diagnosis and deterioration as a consequence of not taking treatment (see sections 3.20 and 3.21) which helped inform the model further.

Figure 15 outlines the problem, the intervention proposed by the film, the consequence of non-action and the proposed outcome that the person will have increased education in order to elicit behavioural change.

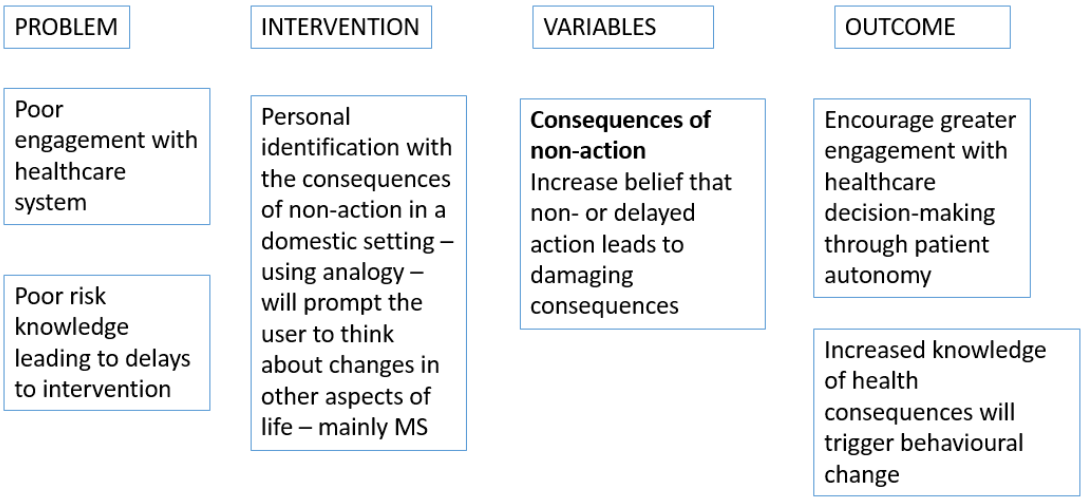

Figure 15: 'Theory of change model' (Aventin et al., 2015) adapted by Wilkie.

4.1.3 Film and use of analogy: why film was chosen

Film has proven to be an effective tool for educating and communicating healthcare information (Jewitt, 2012). Although a number of MS films exist and there is use of analogy to help the user digest complex information (AsapSCIENCE, 2013), the presentation is primarily scientific with an emphasis on the biology of the disease. This approach holds value, but as the previous work identified, pwMS continue to experience DC, poor engagement with the healthcare system and interpretation of disease information - notably treatment risk.

Accepting that film could be a useful vehicle for delivering a message but acknowledging the approach of existing film content that may not work, a different approach has been explored. The result was to present a short film but using a domestic scenario showing damage from delaying action. The rationale for using a domestic setting in a house and car, was that most people could relate to this setup irrespective of their personal circumstances.

Through the use of the analogy described, it was proposed that a person could relate to the situation and understand the meaning underlying the analogy. The overall meaning was that early intervention is important and that this would be conveyed by showing a person leaving for work with the same routine repeated over time. Initially, they do not notice or choose to ignore the signs of wear and tear on their car until the car stops functioning. MS components would then be related to the objects within the film with supplementary information.

The film was driven by two key assumptions inspired by an earlier study created by author Coegnarts (2017) who states:

> 'Meaning in film is metaphorically mapped within our sensory-motor system and that embodied simulation processes in the brain allow for the viewer to infer this meaning from the evidence provided by the film'
> (p:1).

Furthermore, the same author unifies existing models that firstly, people who create art have the aim to transmit embodied thoughts to others. An example of this is conceptual metaphor. Secondly, there are mediums for these thoughts to be conveyed. An example is film. Finally, the viewer infers the embodied thought intended by the creator (Coegnarts, 2017).

Author Sontag (2002) argues 'all thinking is interpretation' (p:91) and therefore use of abstract image and sound is in many ways a natural process (Sontag, 2002). Use of analogy in healthcare is not new but its use varies. Often a military or war scenario is

evoked when illness is interpreted for e.g. a war or battle is waged on a disease (Kostarelos, 2013). This can often have negative connotations and an issue was that the film content had potential to upset, thus it went through ethical review (19/LO/0282) and public and patient involvement (PPI) prior to being released.

4.1.4 Populations to be studied

This chapter presents three new cohorts to be studied which go beyond the timeline of the initial three cohorts described previously. Plotted on to figure 16 introduced in chapter 2, is a cohort comprised of the 'MS Register' with a wider, nationwide demographic. Next, a local MS population (MS outpatients) as part of the Imperial College Healthcare NHS Trust are introduced. Non-MS individuals as part of the 'General Population' were also asked for their opinion as a control group to determine if the findings of the MS cohort were disease-related or if findings could be isolated to this group.

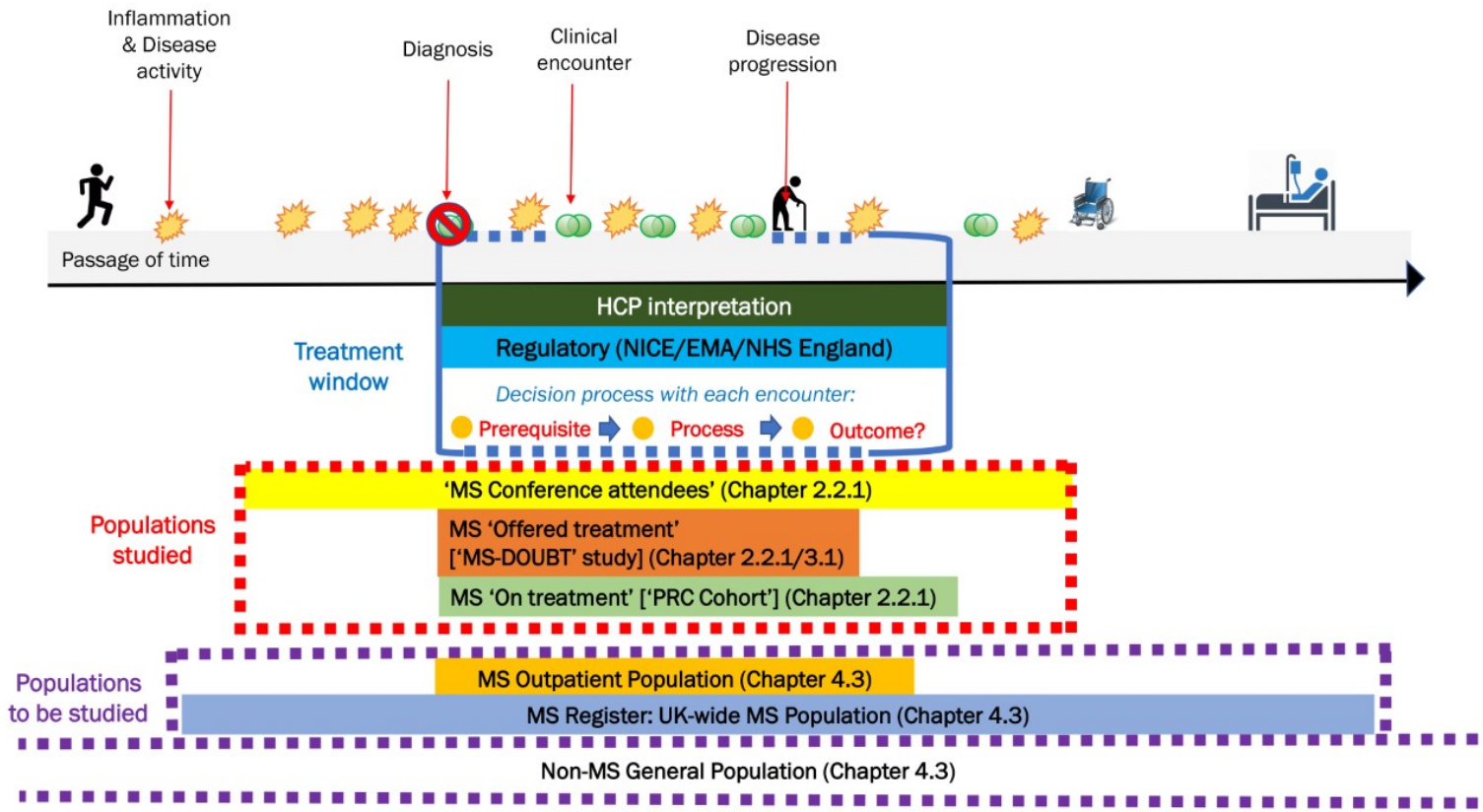

Figure 16: Five MS populations and a general population mapped along the disease timeline

Figure 16 presents the populations previously studied and interpretations of where they lie along a disease/treatment timeline. Three new populations are introduced and described further in the next section.

4.2 Methods

4.3 Participant populations

4.3.1 UK MS Register

Participants were approached through the UK MS Register which has up to 17,000 people currently registered with a UK-wide demographic. By utilising this group, it was expected that the research would reach those who fell outside of the healthcare system and perhaps did not visit the hospital regularly. This was inspired in part by the MS conference attendees population who demonstrated a high level of DC.

Created in 2011 by the Health Informatics Group as part of Swansea University, the MS Register is funded by the MS Society charity. Its aim is to record real world data on pwMS in the UK. The MS Register does this in two ways: pwMS recording information about their MS directly to the MS Register through the website via questionnaires. In addition, there is collaboration with hospitals across the UK to link consented website participants' medical records with user responses (Register, 2019).

PwMS can sign up to the MS Register to provide details about their MS as part of a long term study. Participants already signed up were able to access the film research via a portal. From the portal, participants are able to view research that is available to

them to complete if they wish to. The research was introduced this way; briefly outlining the background to the research and to ask if the person could review the film and website content.

4.3.2 General Population cohort

The 'General Population' cohort included all other visitors to the website and the purpose of this cohort was to act as a comparator (control) group to the UK MS Register. It was also acknowledged in previous chapters the importance of partners as influencers, but also extended family members and friends as part of parties involved in a treatment decision, hence their inclusion.

It was acknowledged that people fall outside of established healthcare systems and there are many approaches to a person's management of their own healthcare hence seeking out information online. One application of this was CCSVI introduced in chapter 1.

Using the internet to deliver healthcare information, there is the potential to reach a far wider audience and inform people who may influence those with MS or have only a passing interest, to the importance of early intervention. The content is purposefully presented in order to be as digestable to as many people as possible. It was also crucial to measure if self-perceived understanding was universal or consistent with an MS audience.

Upon entry to the website, the participants were presented with a disclaimer detailing how their data would be managed as well as a question asking if they had MS or not.

Participation was anonymised so it was not known if the participant was, for example, a healthcare worker.

The content for this was led by information governance at Imperial College London. Again the website was hosted by the UK MS Register with an additional question upon entry asking if the person had MS or not.

Coverage was achieved through the thesis author's social media (Facebook) with an introduction to the research and a web link for people to complete it. People were encouraged to share the research independent of the thesis author using their own newsfeeds or by other means, with friends, family and colleagues.

4.3.3 MS Outpatients cohort

This was achieved through outpatients clinics at Charing Cross and St Mary's Hospitals. The MS Outpatients cohort (referenced as part of the RCT in the research aims) was adapted to include this smaller, sub-cohort of patients based upon the feedback from the MS Register cohort. The General Population cohort was therefore adapted to incorporate some patients with MS from an outpatient setting. The thesis author approached pwMS in-person in clinics about participating in the research**.**

4.4 Film development – the concepts and environment

The thesis author and lead supervisor had previously worked together on films in support of the MS service. Analogy had been explored in one of these films, aimed at an audience participating in a phase II clinical trial of Simvastatin (Chataway et al., 2014) for which the thesis author was trial manager. The purpose of the film was

to present trial results in a simple and concise way to those who had participated in the trial and family members. Analogy was employed utilising a cartoon of a boxing match to show the placebo versus treatment arm. A wire and plug was used to show the damage to the myelin sheath, resulting in messages not getting through to a light bulb and representative of damage to the CNS in pwMS (MSTC, 2013).

As the simvastatin film was well received, further discussions were held as to how a new audience could be targeted. The audience considered and who would get most benefit was considered to be those who were newly diagnosed (within 3 years of diagnosis) or/and treatment naive (incorporating those with longer disease length, potentially). A car engine was suggested by the lead supervisor as a way of portraying an immune system.

A car was chosen as a concept because of its familiarity, popularity and importance to modern society (Dron, 2019) and it has been interpreted in a metaphorical context previously (Wikipedia, 2019), (Baker, 2019). Here it was used as a device that could be linked to other phenomena - in this case to a person's body. The car's body could be manipulated to show deterioration and additionally the car's inner parts (in this case the engine) could be used to portray the immune system. Finally, pollution could result from the breakdown of the car's system internally.

In summary, the car as an object had the potential to embody a number of concepts in one form and additionally, it could be placed within a domestic setting which was central to the narrative.

To illustrate the effects of non-action, an adult female ['the protagonist'] was presented leaving for work over a period of time and failing to notice (or choosing to ignore) signs of wear and tear around her. This would manifest as scratches to her car, rust to her car key and other signs such as leaves falling from a tree that indicate through layering, that there are consequences to non-action.

The film director (James Cook, a former work colleague of the thesis author) was approached about producing the film when the script was at an advanced stage. After meetings and e-mail correspondence, a storyboard emerged drawn by the director, based upon the film script - See figures 17-19.

The film was scripted by the thesis author (see appendix F) and the script went through five revisions until finalised. Only three individuals were involved in the scripting process: the thesis author, James Cook as director and Richard Nicholas as supervisor. The same three were involved in all further revisions of the script.

A meeting was conducted in-person to discuss elements of the film – for example, the characteristics of the main protagonist. A male lead was proposed by the film director on the basis that men could be perceived as more challenging to engage in healthcare decision-making (Wang et al., 2013), (Harvey et al.). However, as three men were primarily deciding the components of the film, there were concerns that this could indicate a gender bias. Additionally, as MS affects women in the UK more than men (Mackenzie et al., 2013), it was decided that it would be more beneficial to engage a greater portion of the MS audience by casting a female lead. Furthermore it was intended that the film's message should aim to engage the newly diagnosed. On this

basis, a female in her thirties was considered most appropriate as this is the demographic presented in the majority of those newly diagnosed (Mackenzie et al., 2013).

In terms of casting, a number of female leads were considered (see casting sheet - appendix G). The thesis author who holds an honorary contract at University College London, independently approached female colleagues based at Queens Square, London, in the MS/neurology field for an independent evaluation of who they felt might be suitable. On this basis, the female lead was chosen. No PPI was conducted prior to the film's production.

However, when the film was still being edited and prior to ethical evaluation, the thesis author approached patients in an outpatient clinic as part of Charing Cross Hospital.

In December 2018, the participants were asked to review the film and website and for general feedback on the process and whether the content was sensitive with the potential to upset participants. Feedback was as follows:

Participant 1

- Confirmed message behind the film was clear and important
- No idea what film was about without the context i.e website.
- Don't understand reference to treatment on film alone but website makes message clear.
- More relevant to him around time diagnosed (2013) versus now.

- Prefers links to sites that are more dynamic/update more regularly but could supply no suggestions for replacements.
- Asked to show film to two grown-up children in their twenties. Await their feedback.
- Did not find it scary or upsetting

Participant 2

- The film works and that it is useful.
- Said the film was about how things deteriorate over the passage of time and that the message behind it is important.
- That it is useful but treatment is not the only option to everyone – diet/lifestyle also significant.
- Could see the value in planting the seed/putting the possibility of managing own's care into a person's mind but not telling someone exactly what to do.
- Said it was a tool that contributes to someone looking up their own health and taking charge in order to ultimately come to an informed decision.

Based on this feedback, there were no identified risks.

Stylistic decisions are discussed in the next section.

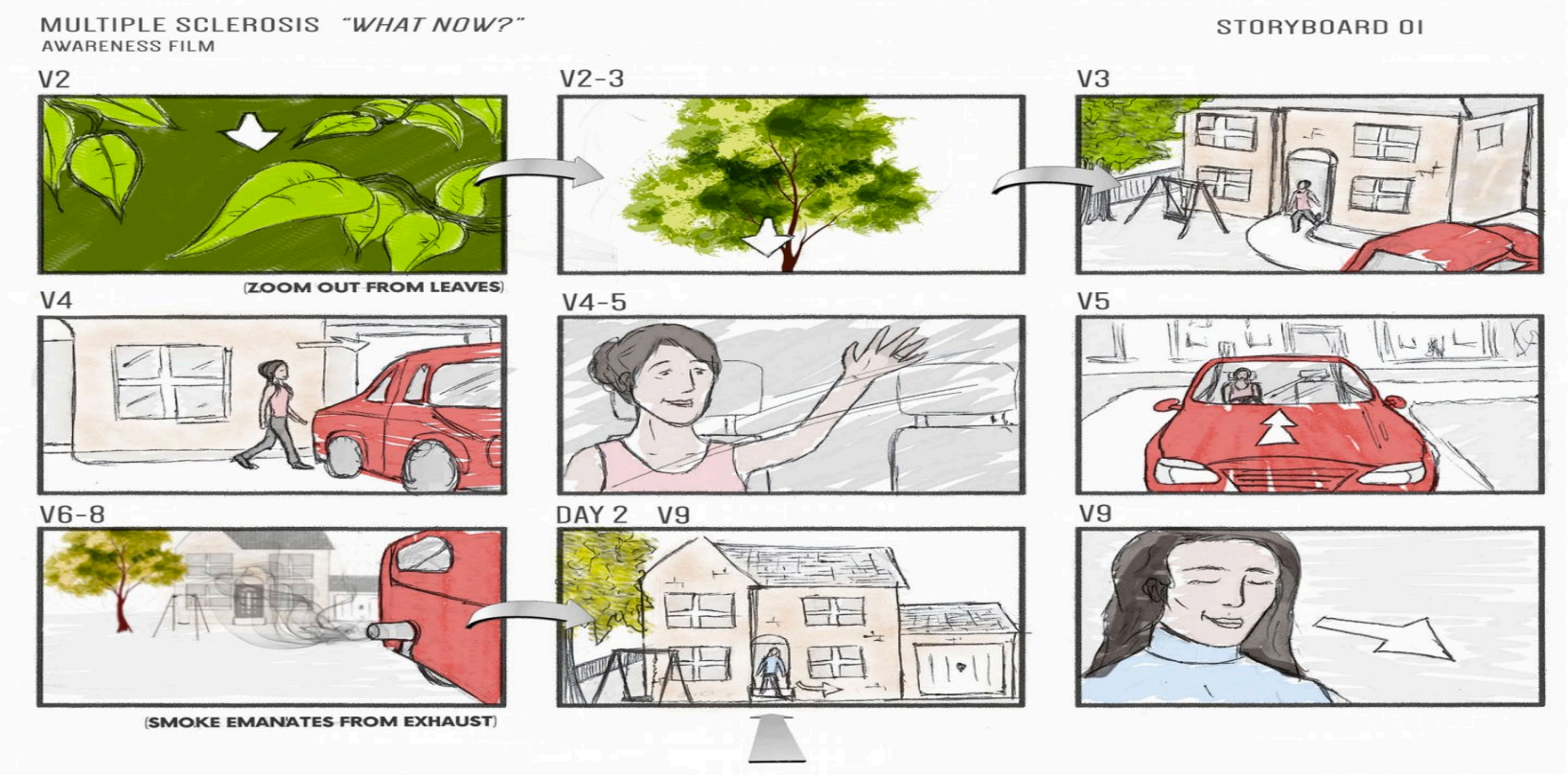

Figure 17: 'Storyboard 1 illustrates no damage'
The tree and environment show no deterioration as the protagonist exits her home

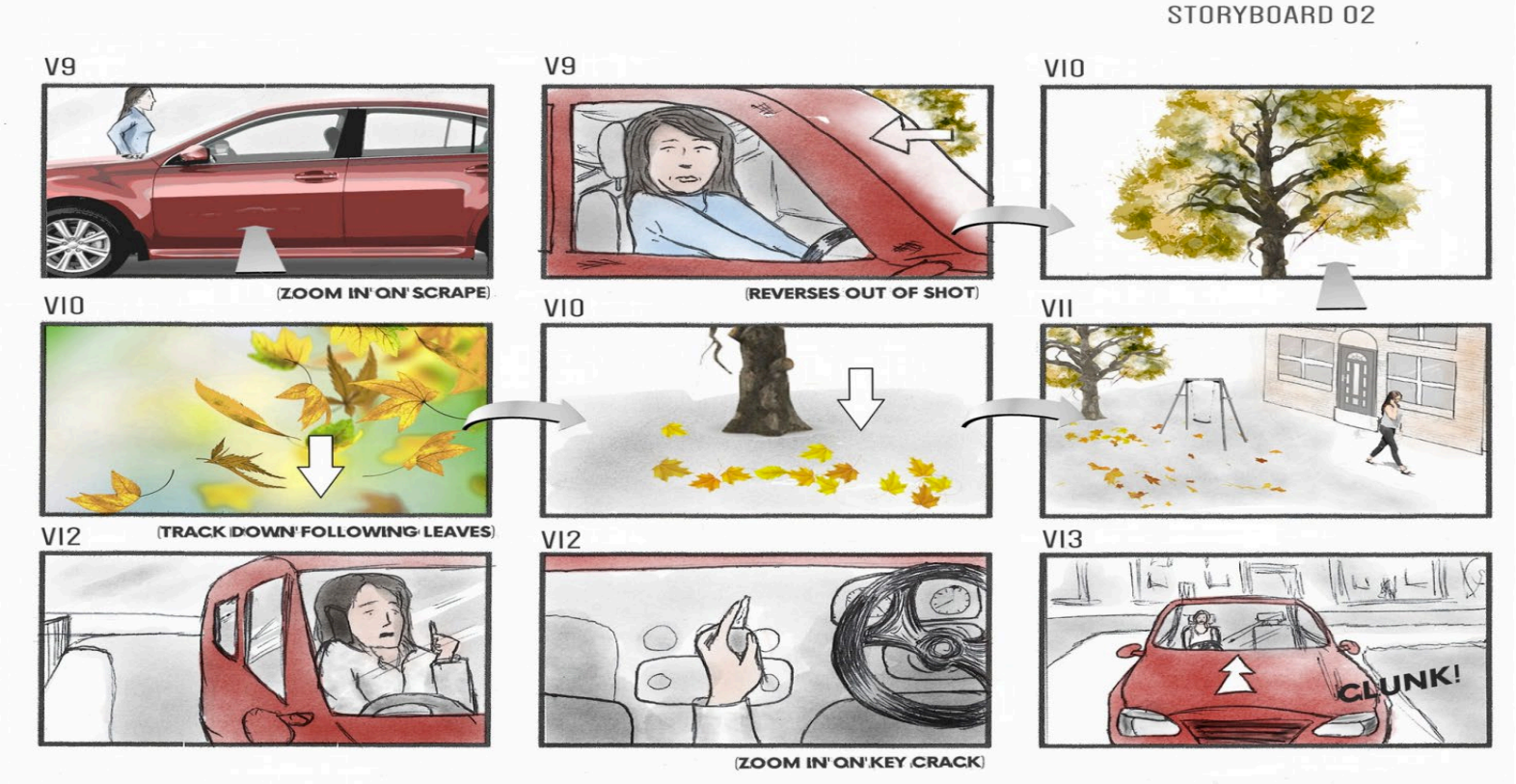

Figure 18: 'Storyboard 2 shows the first signs of damage'
The car shows scratches with rust on the car key and the tree stripped of leaves caused by pollution

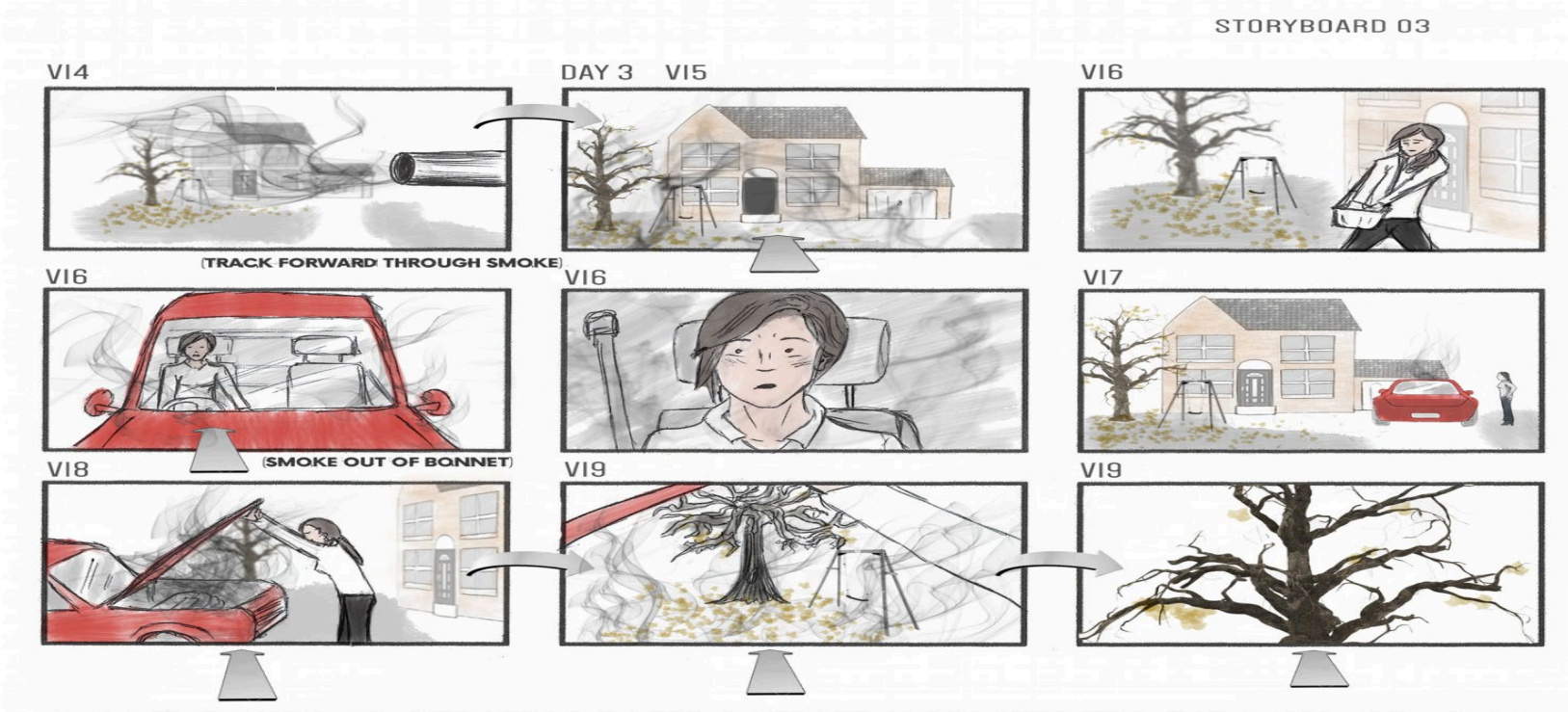

Figure 19: 'Storyboard 3 shows severe effects of non-action'

The scenes portrayed indicate pollution affecting the environment and the car engine failing to work, leading to a tree without leaves and the realisation by the protoganist that non-action previously has led to consequences in the present

The storyboard shows the various components that have been referenced to MS. Four were isolated as a focus of the film. Firstly, the car is representative of the person's body. Within this, the car engine represents the immune system. The pollution represents damage emerging from the immune system and finally the tree represents the CNS which is impacted by the pollution.

4.4.1 House and environment

The presentation of the house was changed a number of times in response to feedback from colleagues when the film's look was still being tested. The original look was considered "too American/Floridian" and a more generic/'European' look that would be familiar to a majority was instead favoured. The thesis author felt it important that the house would need to be a house a European audience (the primary) audience could identify with. The child's swing in the garden indicates that the protagonist has a family, which is also alluded to when she waves off a family member at the beginning of the film. Other styles that were considered can be viewed in Appendix I.

4.4.2 Actor selection

The actor was chosen from a shortlist independent of the thesis author. Criteria was provided to the casting director for a female in her thirties, as this is reflective of the average age and gender of those diagnosed with MS. Colleagues were then approached independent of the thesis author to choose from a shortlist of four people. The clothes were also considered, with a smart look favoured to emphasise that they were a working professional (see appendix G and H for acting shortlist and wardrobe moodboard).

4.4.3 Sound & Music selection

The influence of music on behaviour has a long history. As author Nathalie Nahai demonstrates in 'Webs of Influence' (2017), music can be used as a primer. In a supermarket, French music was piped and more French wine was bought. However, the consumers were not aware of this – the impact can be subconscious and subtle (Nahai, 2012). The music changes half-way through the film to reflect the realisation/ 'epiphany' moment of the protagonist. This approach has been used in film previously where a change in pace or rhythm can reflect a threat (BBC, 2019). In this context, the threat is the consequence of non-action. A decision was made by the thesis author not to use dialogue, voice-over or on-screen captions or text as it was felt that this may detract from the visual message. Owing to the absence of spoken or written dialogue in the film, the music's pace and selection was considered in order to convey the message and the changes throughout the narrative.

4.4.4 Additional Considerations

A decision was made between the thesis author and primary supervisor that PPI could not be used to evaluate the film prior to production as the film did not provide measurable components for e.g. questionnaire items that could be tested and changed based on participant feedback. The content was entirely conceptual and exposing the approach to pwMS before the film's production would have exposed the audience to the intentions before its evaluation.

On the basis that the film should appeal to as wide an audience as possible, elements were kept to a minimum. It was anticipated that ultimately people from many

ethnicities could review the film content For this reason, where English was not a first language or not spoken at all, dialogue and captions were not used.

Music was instead used to convey the change of emotion and pace.

The RIMS group (see section 4.7) were initially used to evaluate if the film's message came across as they were an audience comprising of Europeans for which English was not the first language in the majority present.

The film would not have remained abstract if it had been entirely explained by dialogue and captions within the film itself. Its purpose was to elicit in the viewer intrigue and to encourage them to look at information in order to explain the concepts portrayed and the connections made.

Linking the concepts to MS was achieved through a website (post exposure to the film), and this furthermore allowed for evaluation in which the participants' perceived understanding of the film's concepts could be captured.

The film was produced in a way that meant it could be adapted further and, indeed, the same concepts could potentially be linked to other conditions as the connections to MS are implied with supplementary information (i.e. the website) but never explicitly referenced.

4.4.5 Footage reversal

At the conclusion to the film, the footage is reversed to emphasise to the viewer that by going back in time, they could avoid the future being portrayed, returning themselves to their original state when intervention could have been made before damage had occurred.

4.4.6 Production and Post Production

The film was recorded over one-day using green-screen attended by the thesis author and lead supervisor. Green screen or 'chroma key' is a means to place a generated background in place of the green screen (Wikipedia, 2020b). For this film, a computer-generated background was necessary as the environment required manipulation e.g. leaves falling from a tree and directed pollution towards the tree from the car. This content was edited independently of the thesis author by the film director and a colleague. A number of edits were provided and discussed until a final edit was agreed. Some changes occurred during the process for e.g. the style of house changed, the pollution was increased, scratches on the car were made more prominent and the tree's look was changed to look more radiant at the beginning.

4.5 Website development - prototype

The finished film was embedded within a website created by the thesis author using WordPress v4.9.6 and its purpose was to support the film's content by explaining the film's components in more detail, provide a forum to feedback and to offer further advice and support. The four components (car, tree, engine, pollution) were isolated so the user would be alerted to them (a snapshot of the website can be viewed in

appendix J). The website was adapted by the MS Register independent of the author. The prototype website produced by the thesis author can be viewed at the following link http://www.bcb45a130c98d3b472419a426-15620.sites.k-hosting.co.uk/

The standalone film can also be viewed on YouTube at the following link https://youtu.be/EAi-MlCIJLc

4.6 The website content – adapted by MS Register

The following information is presented 'as seen' by participants across cohorts when accessing the website adapted by the MS Register and which was formerly located at http://www.whatnowms.com when the research was open to research participants. It was not possible to replicate the thesis author's website due to hosting restrictions, hence the content was adapted by the MS Register based on the information as follows.

MS Film

Please complete the survey below.

Thank you!

Please watch the video in its entirety with sound on. NB: music is featured but no spoken word. Please note, that the URL given at the end of this video is not currently live. Please do not follow the link

Engine:

The car engine represents the person's immune system. MS is an autoimmune condition where the immune system malfunctions. Usually the immune system

protects the body against infections and drives the healing process. In a person with MS, the immune system attacks the body when there is no infection present resulting in damage.

Do you understand what the engine represents? [Yes/No]

Pollution:

The pollution represents the chemicals released by the abnormal immune system. These chemicals cause the damage to the axons, synapses and nerve cells as shown by the tree trunk, branches and leaves.

Do you understand what the pollution represents? [Yes/No]

Tree:

The network of axons and nerves and synapses are part of the central nervous system (CNS) represented by the tree's trunk and branches. Axons are the thread-like part of a nerve cell along which signals travel. Synapses are how nerves communicate with each other by means of releasing a chemical. The leaves represent the nerve cells. The nerve cells process our movements and sensations as well as our thoughts and emotions.

Do you understand what the tree represents? [Yes/No]

Car:

The car represents a person's body which can become damaged over time in MS. The scratches on the car represent this damage which the person ignores at first. The outward signs indicate that something is not right with the car/body. The damage

becomes more serious as the film progresses. Finally, the car breaks down.

Do you understand what the car represents? [Yes/No]

More about MS and early treatment intervention

In MS, the immune system attacks the central nervous system (CNS) which includes the brain, spinal cord and optic nerve. There are two main features: relapses and progression, which determine the different types of MS. Relapses are the worsening of neurological symptoms for 24 hours or more with partial or complete improvement over time. Progression is a gradual worsening of these symptoms over time. What we do know is that early intervention is proven to be important in MS, as once the symptoms are established they cannot be reversed. People who are newly diagnosed sometimes delay treatment. This can be because there are no symptoms. Other issues include concerns about the risks of treatment or plans to start a family.

Do you have any comments about early treatment in MS [Yes/No]

Please enter your comments about early treatment in MS below [Freetext response]

More about what the film is about

The aim of the film is to help people understand the importance of early treatment in MS. A young woman has been chosen to play the part of the person with MS because the condition is more common in women and the average age of diagnosis is 30. We have presented a setting that all of us can relate to: the car represents the person's body, the engine represents the immune system, the tree represents the

central nervous system and the pollution represents the chemicals that cause damage. The person ignores the early signs that could have made a difference.

What do you think is the overall message of the film? [Freetext response]

View Useful Information about General Support and Evidence [Yes/No]

General Information and support for newly diagnosed patients (links were provided to the following):

MS Society (UK)

MS Trust (UK)

NHS MS Overview

Shift.MS

National MS Society (US)

Treatment information

MS Decisions Tool

The evidence for early treatment intervention

Guidelines on the pharmacological treatment of people with MS

For further information about any content featured as part of the film or website, you can contact David Wilkie [contact details removed].

4.7 Evaluating the film: pre-study HCP group

In November 2018, the film and prototype website was presented to a group of HCPs attending the RIMS conference in Berg, Germany, comprised of decision experts, neurologists, research nurses and a psychologist in the MS/neurology field. RIMS (Rehabilitation in Multiple Sclerosis) is the European network for best practice and research in MS rehabilitation (RIMS, 2017). Feedback on the film was that the message to consider treatment was strong; that it was not by definition a DA or 'complex intervention' as no options had been offered; however, if it was used as part of an RCT with the support of an MS nurse, then it would become an intervention. MRC framework could also be applied. Context was also emphasised as important. The delegates were also asked to complete self-perceived understanding of the film across the four concepts (see results – table 12).

The main theme that emerged from the comments was that the film's underlying message was about the importance of *early intervention*. Comments included 'No treatment your MS will get worse'; 'The overall message is to inform and educate the patients about treatments and how they can affect their body functions'; If you don't prevent the impact of the disease, you may run out of time later on'. Another theme that emerged from discussion was the need for viewing the film with context in order to be truly impactful.

PPI was carried out prior to ethical review in an MS clinic held at Charing Cross Hospital in London in December 2018. MS participants were asked to review the film and prototype website content. Feedback was generally positive and the message was

said to be clear and understood. The importance of the message was acknowledged alongside the need for presenting the film with appropriate context as previously stated by HCPs – in order to get the message across.

Based upon this feedback, the research proceeded to the next stage. A protocol was created outlining the background to the film, rationale and the research aims. Sponsorship was confirmed by Imperial College London. In tandem, advice was sought from information governance in response to General Data Protection Regulations (GDPR) with reference to confidentiality, data storage and the consenting process. The information stored at the MS Register was confirmed as secure, fully GDPR compliant and the data that resulted was anonymised.

This advice informed the participant documents such e.g. content for entry into the website.

4.8 Ethical approval

Approval for the protocol and related documents was obtained from the London-Bromley Research Ethics Committee (REC ref: 19/LO/0282).

4.9 Evaluating the film: Aims and Objectives

The primary research question was asking if engagement could be measured in pwMS utilising information presented in film-form online. This was to be determined by the outcome measures.

Exploratory aims:

- To explore presentation of information utilising non-scientific metaphor.
- To measure behavioural response across different populations.
- To elicit behavioural change in pwMS to consider early treatment intervention.

Outcome Measures: To quantify user engagement using digital metrics:

Primary outcomes

Primary outcome: **Engagement (All cohorts)**

- The 'viewer retention' i.e. average percent viewed (50%). This is an industry standard and is measured using **averageViewPercentage** (YouTube, 2019), (Bateman, 2018). This will be based on the first, unique view and will be further stratified by YouTube watch page versus embedded video.

Primary outcome: **Nudging (All cohorts)**

- Transfers from video (watch film in entirety?) to website (%). This is measured using **cardClicks** (YouTube, 2019). Film located at https://youtu.be/EAi-MlCIJLc. The referring sites variable can also give this insight recording from which site the user has come.

Primary outcome: **Education (All cohorts)**

- % who interact e.g. click on any answer or any link on site.

Primary outcome: **Understanding (All cohorts)**

- 50% understanding of all users who interact per concept (of four) as defined by a 'yes' answer to each question (necessary knowledge for correct use evaluated between 42.5 % and 57%) (Rubio et al., 2015).

Primary outcome: **Time to treat (Cohort 3 only)**

- To determine if the interventional cohort takes treatment earlier than the standard care cohort as measured by date of recorded intention to treat from date of consultation (30% difference determined by n=50 per arm).

Secondary outcomes

Secondary outcome: **Engagement**

- Number of participants who watch 30 seconds or more of the film (raw view) (Beck, 2015)
- Number of participants who watch the film in its entirety (reached cardClick page).
- Number of likes/dislikes
- Number of shares.
- Number of participants who visit the website.

- Number of participants who complete all feedback at the website.
- Number of participants who complete any feedback at the website.
- The most visited sections of the website.

Participant approach

Eligibility: Cohort: MS Register: self-confirmed MS diagnosis n=250*

Cohort: General Population: no entry criteria**

Cohort: MS Outpatients: self-confirmed MS diagnosis n=250**

Cohort: RCT of MS Outpatients (not performed) n=100***

Exclusion Criteria (Cohort RCT only):

- Currently on or have been on DMT.

Study Duration:

The MS Register cohort data was collected first and data from the General Population and MS Outpatients were collected contemporaneously.

Film Duration: 2 minutes 44 seconds.

* The actual number of participants (n=959) were recruited quicker than anticipated and far exceeded the study target (n=250) The research was halted after one month when this number was reached.

** n=250 incorporated both the General and MS Outpatient populations and was not powered as a result of this change.

*** An RCT was incorporated into the study protocol but not performed owing to the feedback from the MS Register cohort. Also see sections 4.19 and 5.3.

4.10 Accessibility & Platform Delivery

User access to the film was considered. The film was viewed over the internet and accessed by a range of mediums including 'smart phones'. A recent study suggests that pwMS are responsive to this technology (Kehoe, 2017) and it is important that the content can be accessed almost anywhere.

YouTube was chosen as the primary access to the film for its popularity and access to a wide audience. Over 1.9 billion log into YouTube per month. More than 70% of YouTube watches originate from mobile devices (YouTube, 2018).

Additional reasons were described extensively in section 1.13.3.

4.11 Statistical analysis

4.11.1 Demographics / MS Status

For the purpose of stratification to determine from different populations of pwMS how different groups may respond to the film, demographics and information about the person's type of MS, as well their treatment status were obtained. Ethnicity, employment and marital status were also available and used. This pseudoanonymised data was made available by the MS Register who had obtained the demographical information as part of the MS Register's own questionnaires (not collected as part of the PhD). The demographical information could be linked to each user who completed the PhD research but the identity of the user could not be known by the thesis author.

Data are presented as percentages, means and standard deviations as appropriate.

4.12 Quantitative

Ethnicity was coded as 1=White (containing the categories: British, Irish, 'I am White (British, Irish, Other)' | 2=Black (African, Caribbean, 'I am Black or Black British (Caribbean, African, Other)', 'I am mixed (White and Black Caribbean, Black African, Asian)', 'White and Black African', 'White and Black Caribbean' | 3=Other (Another ethnic group, Chinese, 'I am Asian or British Asian (Indian, Pakistani, Bangladeshi'), I would rather not say, Other, 'Other (Chinese, Another ethnic group').

Education as 0=Primary school, 1=Secondary school, 2=occupational certificate/diploma, 3=University bachelor's degree, 4=University postgraduate degree. The 'Other' category was interpreted as 'non-degree' on the recommendation of the MS Register. Education categorisation was informed by the MS Register who have harmonized data to equivalent registers in Germany and the US using various international standards (Salter et al., 2020). For χ^2 analysis, education was further divided by degree educated=1 (3, 4) or non-degree=0 (0, 1, 2).

Total film concept self-perceived understanding was summed 0-4 based on 0=no and 1=yes as answers to the four questions about the film: engine, pollution, tree, car (4 being the highest self-perceived understanding). For χ^2 analysis, understanding was further divided by None to some self-perceived understanding=0 (0-3) or total self-perceived understanding=1 (4).

Gender as 0=Male | 1=Female.

Children as 0=No children | 1=Dependent children | 2=Non-dependent children | 3=children and non-dependent children.

MS type: 1=RRMS/CIS=1 | 2=SPMS | 3=PPMS. For χ^2 analysis, MS type was recoded as 0=Relapsing (1) or 1=Progressive (2, 3).

Disease duration was worked out by knowing the person's age now subtracted from their age at diagnosis. It was further divided by 0=newly diagnosed (0-3 years) and 1=4 years or more.

Treatment status was defined as 0=Not currently on treatment | 1=currently on treatment (at the time the questionnaire was completed).

HADS Depression and Anxiety scores were summed as per previous chapters. The scores were further divided by not depressed (scores $\leq$10) or depressed $\geq$11.

Occupation separated into three categories as follows: 3=Managers, Directors and senior officials (e.g. Office, IT, Healthcare or other managers) | 3=Professional Occupations (e.g. Chemists, Dentists, Doctors) | 2=Associate professional and technical occupations (e.g. Nurses, Laboratory technicians, IT Support, Radiographers, Artists, Authors) | 1=Administrative and secretarial occupations (e.g. Clerks, Secretaries, Personal Assistants, Receptionists) | 1=Skilled/trade occupations (e.g. Farmers, Electricians, Industrial Operators, Plumbers, Mechanics, Aircraft Engineers, Painters) | 1=Caring, leisure and other service occupations (e.g. Healthcare, Childcare, looking after animals, housekeeping and hairdressing) | 1=Sales and

customer service occupations (e.g. Sale and Retail assistants, Call centre workers, Debt collectors, Housekeepers) | 1=Process plant and machine operatives (e.g. Machine Operators, Plant Workers) | 1=Elementary occupations (e.g. Labourers, Waitresses, Porters, Bar Staff, Shelf Filler, Traffic Wardens).

Employment defined as 0=Not In Productive Economic Activity (NIPE) (Engaged in voluntary work, In Formal Education, Looking after my home/family, Not applicable, On a government training scheme, Other, Permanently sick/disabled, Retired, Temporarily sick/disabled, Unemployed | 1=Regular Paid Employment Part Time, Self Employed Part Time or Full Time (Regular Paid Employment, Regular Paid Employment Full Time, Self Employed Full Time | Regular Paid Employment Part Time.

Employment/Occupational classification was informed by statisticians based at the MS Register. Their data classification was further informed by the International Labour Organisation (ILO, 2020).

Wordclouds were generated using Python Version 3.7.3.

SPSS Version 26 and Microsoft Access 2016 were used for statistical analysis.

Film analytics

Viewer retention determined using the variable averageViewPercentage (YouTube Analytics).

Qualitative

Each user's comment was interpreted as positive, negative or neutral by the thesis author ('researcher 1') and then these responses were hidden from an independent researcher ('researcher 2') who performed the same analysis in an attempt not to bias the data. Every comment was then analysed by the author as 'related' or 'unrelated' to the question being asked, as well as categorised by visceral or non-visceral (positive, negative or neutral).

Next, the user comments were reviewed for codes that were then grouped as themes. Three columns were created by both researcher 1 and 2 and comments summarised or abbreviated in order they were recorded to categorise into codes. Thematic analysis (Braun and Clarke, 2006) was employed to further categorise into subthemes and then themes that could incorporate all of the subthemes became overall themes, consistent with qualitative methods described in chapter 3. The subthemes were discussed between researcher 1 and 2 until consensus was reached. For example, a subtheme called 'Recognise signs of MS' was incorporated into another theme called 'Represents MS' and themes 'doesn't aid decision making' and 'not useful for newly diagnosed' were combined into 'value of research (negative)'.

Attitude was coded as 1=Negative | 2=Neutral | 3=Positive. For χ^2 analysis, Attitute was further divided by Negative (1) or Neutral/Positive (2, 3).

There was further classification by attitude and visceral direction coded as 0=Negative & Non-Visceral | 2=Neutral & Non-Visceral | 4=Positive & Non-Visceral |

1=Negative & Visceral | 3=Neutral & Visceral | 5=Positive & Visceral. In order to isolate the positive-visceral and negative-visceral groups, the data was recoded for further analysis as Non-visceral (all)=0 (0, 2, 4), Positive/Neutral Visceral=1 (3, 5) and Negative/Visceral=2 (1).

Visceral was defined as an emotional response (positive or negative) to the film defined as deeply emotional (Cambridge, 2019). Examples of a visceral-negative response included "this [film] would have scared me"; "I find this film overly patronising"; "This film was depressing"; "scary…too hard hitting"; "MS is a disease that will make you die and crack up. Only for pretty, rich, white women. It is also dishonest in its implication that early treatment will put all right. Truly awful film"; "patronising and irrelevant"; "the music made me feel sad"; "If I was shown this film I would of thought it was ridiculous"; "grim and depressing!".

There was a 90% agreement in the comments made: positive, negative or neutral as interpreted by researcher 1 (the thesis author) and compared to researcher 2 (independent researcher). Researcher 2's preference was followed through to analysis to limit bias.

4.13 Results - MS Register cohort

4.14 Demographics

Demographical data was available for the MS Register cohort only. In summary, the majority of respondents were female (74%), in their fifties (37%), of white ethnicity (94%) with RRMS (58%). Most people identified as having a partner (84%). Additional demographical and MS characteristics for this cohort can be viewed in table 11 (over-page). See figure 20 for flowchart of participants.

Table 11: Demographical and MS characteristics of 'MS Register' Cohort

MS-Film Parameter		MS Register Cohort frequency, % (n=959)
MS Type	RRMS/Benign	531, 58.1%
	SPMS	264, 28.9%
	PPMS	119, 13.0%
	Missing	45
MS Diagnosis	≥4 yrs	789, 83.5%
	≤3 yrs	156, 16.5%
	Missing	14
Gender	Female	706, 73.6%
Age	20-29	18, 1.9%
	30-39	97, 10.1%
	40-49	198, 20.6%
	50-59	357, 37.2%
	60-69	235, 24.5%
	70-79	52, 5.4%
	80+	2, 0.2%
***Ethnicity**	White	895, 93.7%
	Black	5, 0.5%
	Other	55, 5.8%
	Missing	4
Marital Status:	With Partner	748, 84.2%
	Without Partner	140, 15.8%
	Missing	71
	No Children	401, 45.2%
	Dependent Children	186, 20.9%
	Non-dependent Children	238, 26.8%
	Children and non-dependent Children	63, 7.1%
	Not known (Missing)	71
Employment Status:	Regular paid employment	285, 32%
	Self-employed	69, 7.8%
	Temporarily sick/disabled	15, 1.7%
	Home/Family-maker	39, 4.4%
	Voluntary work	12, 1.3%
	Unemployed	28, 3.1%
	In formal education	6, 0.7%
	Retired	249, 28%
	Permanently sick/disabled	170, 19.1%
	Other/Not working	12, 1.3%
	Not Applicable	5, 0.6%
	Missing	69
Education:	Secondary School	163, 18.3%
	Occupation certificate/diploma	299, 33.5%
	University Bachelor's degree	207, 23.2%
	University postgraduate degree	150, 16.8%
	Other	73, 8.2%
	Missing	67

On Treatment		255, 26.6%
HADS	**Anxiety** **Depression**	653, 6.61, 4.495 653, 6.89, 4.534

*White (inc. British, Irish, 'I am White (British, Irish, Other)'
Black (African, Caribbean, 'I am Black or Black British (Caribbean, African, Other)', 'I am mixed (White and Black Caribbean, Black African, Asian)', 'White and Black African', 'White and Black Caribbean'
Other (Another ethnic group, Chinese, 'I am Asian or British Asian (Indian, Pakistani, Bangladeshi', I would rather not say, Other, 'Other (Chinese, Another ethnic group'
**N, Mean, SD.

4.14.1 Access

The film was accessed 961 times between 20th May – 24th June, 2019. Two of the respondents were dismissed from the analysis as they were recorded as 'test' responses, leaving 959 responses that were usable. The majority of people in the overall cohort accessed the research through a computer (62%), followed by mobile phone (22%) and tablet (16%).

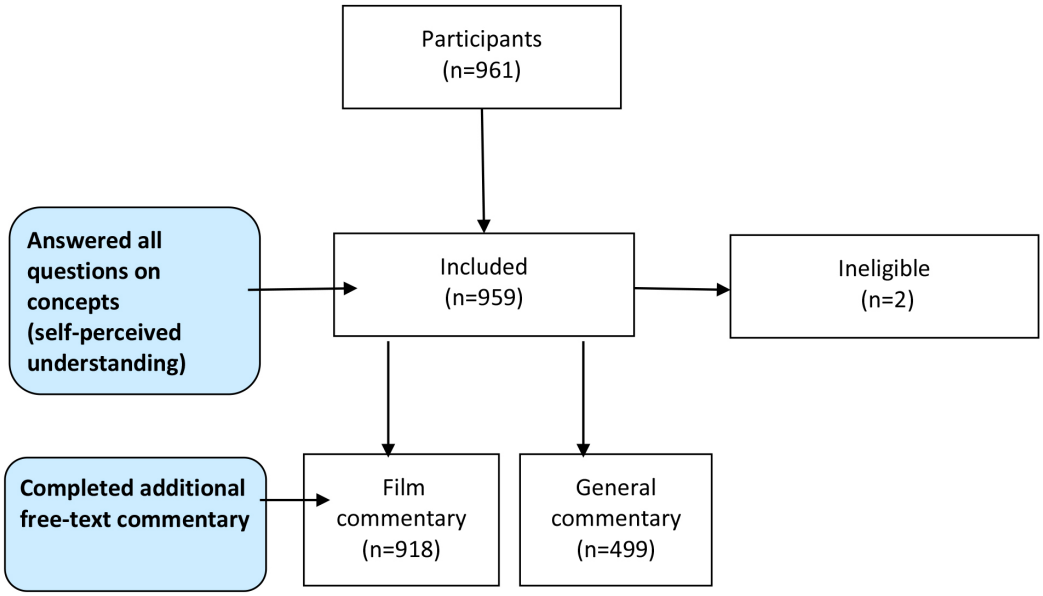

Figure 20: Flowchart of MS Register participants

4.14.2 Engagement

Average viewer duration in the MS Register cohort was 2 minutes: 37 seconds equivalent to 95.7% as measured using YouTube analytics. Six hundred and ten views were recorded of which 582 were unique. Therefore 582/959 views resulted in a 61% retention. A 50% retention was expected so this result exceeded the research aim of 50% (p=<.000, Binomial test).

4.14.3 Self-perceived Understanding

100% of users answered all four questions about the film and 757/959 (78.9%) understood all four concepts confirming total self-perceived understanding. A 50% self-perceived understanding was expected meaning that the result exceeded the research aim of 50% (p=<.000, Binomial test).

4.14.4 Self-perceived understanding of concepts

Within the MS Register cohort, the car was the most understood concept in 888/959 (93%) followed by the engine 872/959 (91%), Tree 820/959 (86%) and finally Pollution 792/959 (83%). The majority (79%) understood all concepts (4/4) (see Table 12).

Table 12: Concept self-perceived understanding measured across cohorts

Self-perceived Understanding	Pre-study HCP cohort (n=12) Yes answers, %, missing (as applicable)	MS Register cohort (n=959) Yes answers, %, missing (as applicable)	MS Outpatients cohort (n=42) Yes answers, %, missing (as applicable)	General Population (n=148) Yes answers, %, missing (as applicable)
Engine	11, 92%,	872, 91%	33, 79%	140, 95%
Pollution	8, 67%	792, 83%	33, 79%	139, 94%
Tree	8, 73% 1 missing	820, 86%	33, 79%	139, 94%
Car	9, 82% 1 missing	888, 93%	37, 88%	142, 96%
0/4 concepts	*NA	42, 4.4%	4, 9.5%	3, 2.0%
1/4 concepts	*NA	38, 4.0%	2, 4.7%	3, 2.0%
2/4 concepts	*NA	60, 6.3%	3, 7.1%	5, 3.4%

3/4 concepts	*NA	62, 6.5%	4, 9.5%	1, 0.01%
4/4 concepts	*NA	757, 78.9%	29, 69.0%	136, 91.9%

*The HCP cohort (the 'RIMS group' referenced in section 4.7) response was measured as part of the prototype website. The concept self-perceived understanding per individual is therefore not available.

University Education is associated with less self-perceived understanding of the film concepts in the total MS Register population

To determine what variables may drive self-perceived understanding, a multivariate analysis was conducted in the complete responding population (n=959) with 'self-perceived understanding' (defined by 0-4 concepts) as the dependent variable and the following covariates: Age Now, MS Duration, MS Type, Gender, Ethnicity, Education (dichotomously graded: degree/non-degree), Employment status, Occupation, Household, Number of children, treatment status, HADS depression and anxiety scores.

'Education' was associated with 'self-perceived understanding' (n=892, adjusted R^2 0.023, p=0.000). This meant having less education was associated with increased self-perceived understanding of the film. A one point increase in education was associated with a .170 reduction in self-perceived understanding. See table 13.

The variables 'Education' and 'Attitude' were combined to determine if they were interacting. A multivariate analysis confirmed that they were independently associated with self-perceived understanding and that there was no interaction occurring between the two. HADS Anxiety and Depression were added to the model (n=607) and these were not significant.

Table 13: Multivariate analysis to determine variables associated with self-perceived understanding

	B (95% CI lower, upper), p	
Factor	**Self-perceived Understanding**	**Self-perceived Understanding with Attitude**
Education	-.344 (-.488, -.200), 0.000	-.205 (-.347, -.062), 0.005
Attitude (Negative/Neutral/Positive)	Not included	.781 (.631, .932), 0.000

Those with negative commentary have less self-perceived understanding of the film

The multivariate analysis was re-run using the same covariates above; this time including the covariate 'attitude' of users (negative, neutral, positive) as interpreted by an independent researcher. This time the result showed 'education' as significant alongside 'attitude' (n=857, adjusted R^2 0.126, p=0.000). This meant those with less education and who commentated positively, were independently associated with increased self-perceived understanding of the film. See table 13.

Additional analysis was undertaken by defining education as degree/non-degree level and self-perceived understanding (1=all 4 concepts understood) or none/some self-perceived understanding (0=0-3 concepts understood). Again it was found that having a higher education was significantly associated with less total self-perceived understanding (2x2 χ^2 2-tailed Fishers Test p=0.000). See Table 14.

Table 14: MS Register: Film self-perceived understanding measured by subgroups

Subgroups were analysed to determine if there were any significant differences in self-perceived understanding. Self-perceived understanding here was measured by total self-perceived understanding (4) versus some or no self-perceived understanding (0-3). Subgroups were then further grouped as indicated in the final column. Significant results are emboldened in the final column.

	Film Self-perceived Understanding (Total versus some/no understanding), n, %						
Subgroups	**0**	**1**	**2**	**3**	**4**	**Total n= 959**	**N missing, data groups and test used, p-value**
Education (secondary school)	5, 3.0%	3, 1.8%	10, 6.1%	8, 4.9%	137, 84%	163	**67 missing, Non-degree+** self-perceived **understanding 81/381 vs. Degree/** self-perceived **understanding 104/253 2x2 χ^2, 0.000**
Education (occupational certificate/diploma)	7, 2.3%	12, 4.0%	18, 6.0%	18, 6.0%	244, 81.6%	299	
Education (other)	2, 2.7%	2, 2.7%	1, 1.3%	4, 5.4%	64, 87.6%	73	
Education (degree-level)	13, 6.2%	8, 3.8%	17, 8.2%	19, 9.1%	150, 72.4%	207	
Education (Post-graduate)	15, 10%	11, 7.3%	10, 6.6%	11, 7.3%	103, 68.6%	150	
Newly diagnosed (0-3 years)	3, 1.9%	6, 3.8%	12, 7.6%	11, 7.0%	124, 79.4%	156	14 missing, 0-3 years+ self-perceived understanding 32/124 vs 4 years or more+ self-perceived understanding 168/621 2x2 χ^2, NS
Diagnosed 4 years or more	39, 4.9%	31, 3.9%	47, 5.9%	51, 6.5%	621, 78.7%	789	
Negative	38, 13.1%	27, 9.3%	24, 8.3%	19, 6.5%	181, 62.6%	289	**41 missing, 2x2 χ^2 Negative+** self-perceived **Understanding 108/181 vs. Positive/Neutral** +self-perceived **Understanding**
Positive/Neutral	4, 0.6%	11, 1.7%	33, 5.2%	39, 6.2%	542, 86.1%	629	

							87/542 2x2 χ^2, 0.000
MS type (relapsing)	24, 4.5%	23, 4.3%	36, 6.7%	39, 7.3%	409, 77.0%	531	45 missing, Relapsing MS+ self-perceived Understanding 122/409 vs. Progressive MS+ self-perceived Understanding 74/309 2x2 χ^2, NS
MS type (progressive)	18, 4.6%	14, 3.6%	22, 5.7%	20, 5.2%	309, 80.6%	383	
Male	14, 5.5%	10, 3.9%	11, 4.3%	18, 7.1%	200, 79%	253	Male+ self-perceived Understanding 53/200 vs. Female+ self-perceived Understanding 149/557 2x2 χ^2, NS
Female	28, 3.9%	28, 3.9%	49, 6.9%	44, 6.2%	557, 78.8%	706	
Age 20-29	1, 5.5%	0, 0.0%	0, 0.0%	4, 22.2%	13, 72.2%	18	Age 20-39+ self-perceived Understanding 27/88 vs. Age 40-59+ self-perceived Understanding 122/433 vs. Age 60-89+ self-perceived Understanding 53/236 2x3 χ^2, NS
Age 30-39	2, 2.1%	4, 4.1%	9, 9.2%	7, 7.2%	75, 77.3%	97	
Age 40-49	12, 6.0%	11, 5.6%	14, 7.1%	14, 7.1%	147, 74.2%	198	
Age 50-59	17, 4.8%	16, 4.5%	19, 5.3%	19, 5.3%	286, 80.1%	357	
Age 60-69	8, 3.4%	5, 2.1%	15, 6.4%	17, 7.2%	190, 80.8%	235	
Age 70-79	2, 3.8%	2, 3.8%	3, 5.8%	1, 1.9%	44, 84.6%	52	
Age 80-89	0, 0%	0, 0%	0, 0%	0, 0%	2, 100%	2	
White	40, 4.4%	35, 3.9%	57, 6.3%	54, 6.0%	709, 79.2%	895	4 missing, White+ self-perceived Understanding

Other	2, 3.3%	3, 5%	3, 5%	8, 13.3%	44, 73.3%	60	186/709 vs. Other+ self-perceived Understanding 16/44 2x2 χ^2, NS

NS=Not significant

Eighty-one of 381 (22%) were without a degree education and had no to some self-perceived understanding as measured by 0-3 concepts understood. By comparison, 104/253 (41.1%) had a degree education and no to some self-perceived understanding (2x2 χ^2, p=0.000). Negative attitude and no to some self-perceived understanding was present in 108/181 (59.7%) compared to those with a positive-neutral attitude in 87/542 (16.1%) (2x2 χ^2, p=0.000). Both results were statistically significant showing that those without a degree education were more likely to understand the film concepts and those with a positive-neutral attitude towards the film were more likely to understand it. No differences were observed when self-perceived understanding in the following subgroups' was measured: age, ethnicity, gender, MS type. See table 14.

The individual film concepts were less understood by those who were degree educated

Each concept was individually examined in the total population (n=959). All four concepts were less understood by those in the degree educated group when compared with the non-degree group: car (p=<0.0003), tree (p=<0.0001), pollution (p=<0.0001), engine (p=<0.0001) (all results 2x2 χ^2 2-tailed Fishers Test). This indicated that degree level education was associated with less self-perceived

understanding of all four concepts presented in the film.

Response to the film - free text commentary

There were two optional questions asking users for their opinion utilising free text. The first asked about their opinion of the film ('film commentary') and 918/959 responded (95.7%). There was a second free text question ('general commentary') asking if there were any further comments the user would like to make with reference to early intervention with 499/959 (52.0%) responding. Word count was recorded. Of the film commentary responses (n=918), the mean was 37.82 (SD 47.322). Of the general commentary responses (n=499), the mean was 60.41 (SD 56.348). The result was not normally distributed. A t-test was performed and the result showed a significant difference between the two groups (Kolmogorov smirnov test, p=0.000). See figures 21-22.

The characteristics of the subgroup (n=499) who commented a second time were analysed to determine if there were attributes unique to this cohort. The majority were female (74.9%) had RRMS (57.1%) a disease duration of 4≥ years (83.6%), not on treatment (74.3%) and a total self-perceived understanding of the film concepts (4/4) was present in 76.2%.

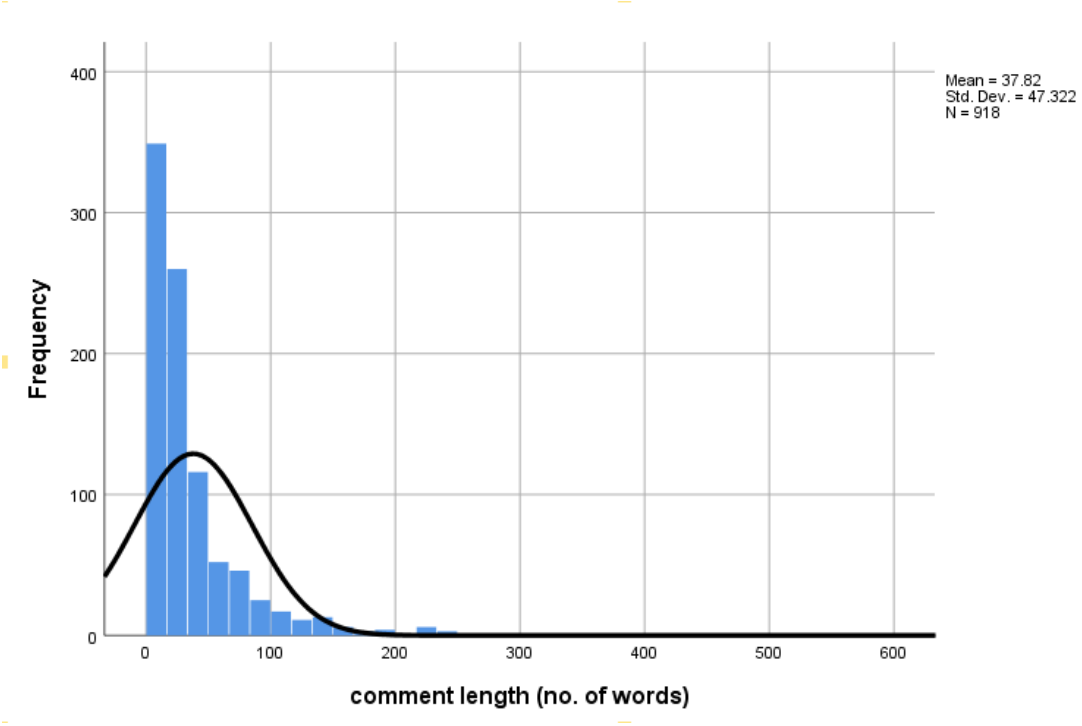

Figure 21: 'Distribution of word counts for the film commentary'

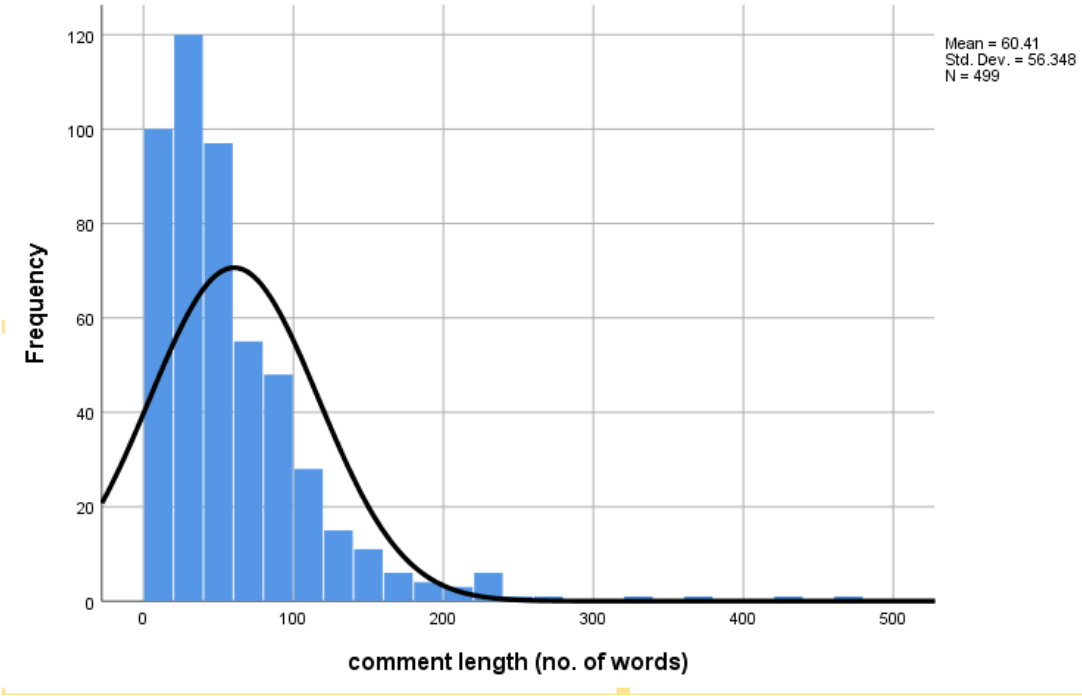

Figure 22: 'Distribution of word counts for the general commentary'

Of those who provided commentary about the film in the total population, 289/918 (31.4%) of the responses were negative as interpreted by thematic analysis.

Negative interpretation was isolated to include only commentary associated with the film content and could manifest across different themes. These included stylistic interpretation e.g. “Too abstract”, “Crayon effect interferes with message” and “music suggested a rose-tinted view of life”. Examples of lack of understanding included: “confusing”, “Unclear aspects” “Tree represents seasons passing” to “more context needed”.

There was an association with negative commentary and degree-level education. One-hundred and five of 328 (24%) of the non-degree group commentated negatively compared to 147/206 (42%) of the degree educated group (p=0.000).

There was also a visceral reaction representative of a more personal/emotional reaction. Fifty-nine of 918 (6.4%) of all MS Register film commentary responses were interpreted as visceral-negative. In contrast, six responses (0.01%) were interpreted as visceral-positive.

Those who had a negative-visceral response still had a high self-perceived understanding of the film. Of this subgroup, 40/59 (68%) had a maximum (4/4 concepts) self-perceived understanding of the film. When the visceral-negative subgroup was isolated and split by education (non-degree (14/44) versus degree (36/22)), those with a degree-level education were more likely to comment negatively about the film (2-tailed Fisher’s Exact χ^2 Test p=<.0001).

Those with a longer disease duration are more likely to be older, on treatment, have progressive disease and to provide a visceral-negative response

There were significant differences in MS type, Age, Treatment status and Visceral-Negativity between the diagnosis cohorts. The visceral-negative subgroup was further split by disease duration 0-3 years: 9/58 (16%) versus 4 years or more: 49/58 (84%). This meant that those in the group diagnosed 4 years or more had a greater proportion of people with progressive MS, aged over 40, on treatment with commentary that was more visceral-negative than the newly diagnosed subgroup. All the characteristics described were statistically significant - see table 15.

Table 15: Characteristics of diagnosis subgroups (MS Register)

Characteristic	Diagnosed 0-3 years (n=156), n (%), missing (if applicable)	Diagnosed ≥4 years (n=789), n (%), missing (if applicable)	p-value
Female	121 (78%)	576 (73%)	NS
Ethnicity White	144 (94%), 2 missing	738 (94%), 2 missing	NS
Relapsing MS	118 (77%), 2 missing	409 (55%), 39 missing	<.0001
Age 20-39	52 (33%)	61 (8%)	<.0001
Degree educated	51 (41%), 31 missing	304 (45%), 106 missing	NS
On treatment	31 (20%)	223 (28%)	0.03
Total self-perceived understanding	124 (80%)	621 (79%)	NS
Negative	38 (26%), 8 missing	248 (33%), 32 missing	NS (0.08)
Subcohort	n=58		
Visceral negative	9 (16%)	49 (84%)	<.0001

Differences are seen when commentary is split by disease duration and visceral response

Wordclouds were generated to determine if differences could be seen in commentary between the disease duration subgroups. When the total MS Register population was split by disease duration (diagnosis (dx) 0-3 years vs. ≥4 years or more), the commentary fields were compared showing similarity between words used in the 'visceral-negative (no)' subgroups for both commentary questions. When the dx subgroups were further split by visceral-negative reaction, differences were seen.

In figure 23, in the 'visceral-negative (no)' arm of the film commentary (n=847), there were similarities between disease durations with an emphasis on the message of the film coming through: 'car' (representing the person's body) and 'message' in the context of the underlying message of the film being early intervention, were the most frequently cited words.

However, when the 'visceral-negative (yes)' subgroups were isolated by disease duration, differences were seen. To gain further insight, the two most popular words: 'message'/ 'early' for dx (≥4 yrs), and 'video'/'something' (0-3 yrs) are presented in table 16 and provide context for the words being used.

In figure 24, the 'visceral-negative (no)' arm of the general commentary (n=451), showed similarities between the long and short disease durations with emphasis on 'early' and 'diagnosed', reitering the importance of this time period to pwMS. 'Early' and 'DMT' were the most frequently cited words in the visceral-negative (yes) subgroup of longer disease duration, which again indicates the message came through

– however, the context was complicated by personal experience. In the visceral-short duration MS subgroup, ‘diagnosis/diagnosed’ was the prevailing theme, in the context that early diagnosis is important. The visceral element can be explained by frustrations with the diagnosis process, mainly delays. See table 16.

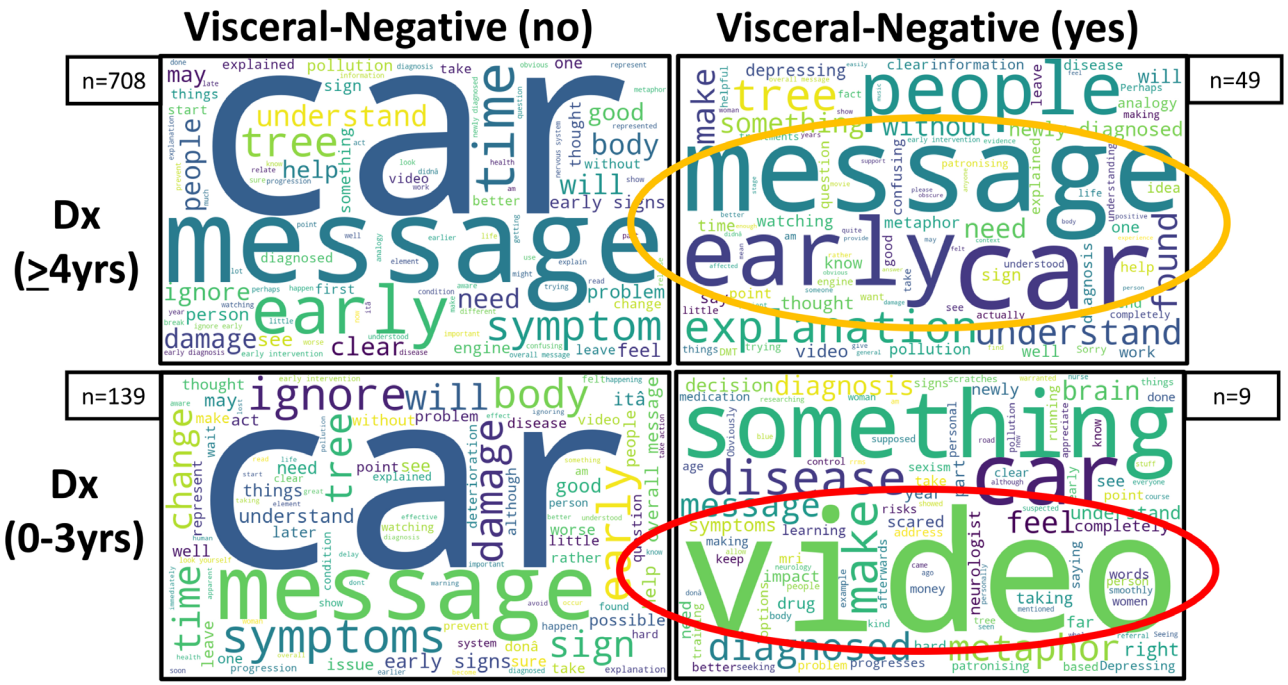

Figure 23: 'Film commentary word cloud split by disease duration and visceral-negative subgroups'

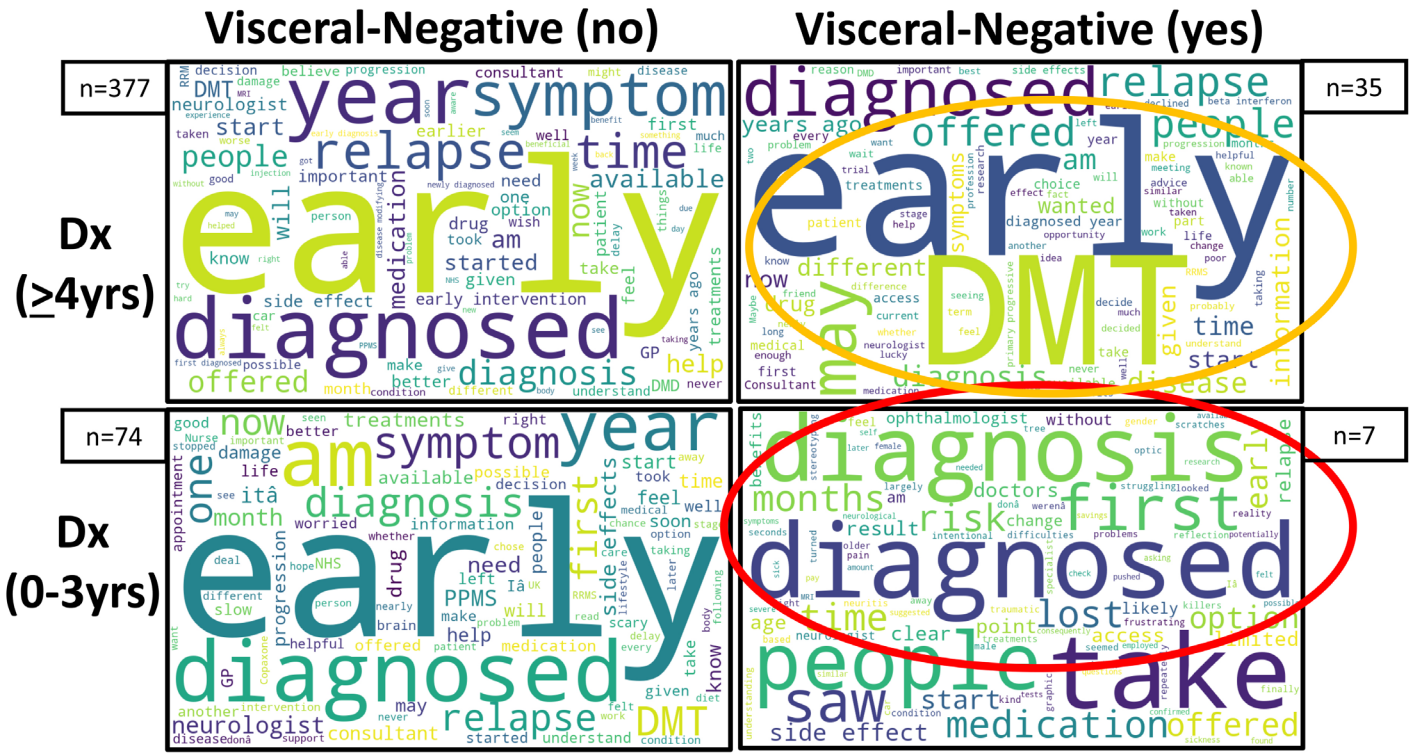

Figure 24: 'General Commentary wordcloud split by disease duration and visceral-negative subgroups'

Table 16: Film & General Commentary split by time since Dx and visceral-negative response

	Film commentary	
	Visceral-negative (yes) examples of words in context	
Dx (≥4yrs)	**'Message'** The overall **message** was one of doom and gloom and inevitability; The overall **message** was that MS will get you in the end!; …the timing of the **message** for the individual would be key because it may push some newly diagnosed people over the edge…; The **message** might be something like early treatment helps prevent or limit damage that MS does to your body due to the faulty immune system. But I found that **message** opaque at best; I think the **message** is being conveyed in the wrong way.	**'Early'** Scary…I really think this film's a bit too hard hitting for someone who has only recently been diagnosed. May a bit more emphasis on the positives of **early** adoption of DMDs MS is a disease that will make you die and crack up. Only for pretty, rich, white women. It is also dishonest in its implication that **early** treatment will put all right.
Dx (0-3yrs)	**'Video'** Whilst I can see what this **video** is saying, I personally feel it would have scared me too at point of diagnosis…Seeing this **video** I think would have scared me into a hard drug whilst learning about the disease…; This **video** does not address in any way the negative impacts the drugs can have and the impact that has on the decision making process; If it wasn't for the descriptions below the **video**, I wouldn't have known what was going on.	**'Something'** The video sends out the message to take care of **something** before it progresses; To do **something** as soon as possible. But to do **something** you need to know there is **something** to be done. I didn't ignore early warning signs, went to GP on numerous occasions, and it wasn't until I was diagnosed that I could do **something**. The film implies to me that I have done **something** wrong in ignoring signs and feels like it is putting some of the blame on me, when this isn't the case; I don't believe it makes any sense, I'd scrap this video completely and work on **something** far more obvious. If you do insist on using a car and pollution as an example, use **something** mechanical with the car rather than scratches…
	General Commentary	
Dx (≥4yrs)	**'Disease Modifying Therapy (DMT)'** When I was first offered DMT, the information was very unbiased and you were left to work it out for yourself if you wanted **DMTs**. At that time, I wanted to start a family so I declined **DMTs**; Why are **DMTs** not offered to people who have had RRMS for a while and who are still having relapses?; Although the attitude to early treatment may have changed, the NHS website is lukewarm about **DMTs** and puts them at	**'Early'** I was not told about **DMTs** being helpful when I was in **early** stage MS I have had RRMS for 8 years and never had a relapse since starting **early** treatment; A friend was diagnosed this year, she understands how important it is to get **early** treatment wants some, but has been told she is not eligible for any but Beta interferon – probably – and should hold off taking any!;

	the end of a very long list of treatments for current problems.	This doesn't appear to be the recommended response now, with evidence that **early** treatment is most effective to delay longer term issues.
Dx (0-3yrs)	**<u>'Diagnosis/Diagnosed'</u>** My **diagnosis** was traumatic as a result of the first doctors I saw (I was **diagnosed** at point of optic neuritis which turned out to be my seconds relapse by ophthalmologists) had a limited understanding of the condition; I had my treatment as soon as I was **diagnosed**, if I had been **diagnosed** sooner, I could have prevented some of the long term damage I have to my mobility. Just as important as early treatment is early **diagnosis**.	

Table 17: Attitude measured across cohorts

The findings show a significant difference in negative commentary in the MS Register cohort compared with the General Population cohort. This shows negative commentary is associated with the MS Register cohort but there were no significant differences when compared to the other cohorts.

Attitude	*HCP group, (n=6) n, %	MS Register, (n=918) n, %	MS Outpatients, (n=50) n, %	General population, (n=182) n, %	P-value comparing cohorts (2x2 χ^2 comparing Negative vs. Positive/Neutral
Comments Negative	1, 17%	289, 31.4%	8, 23.5%	18, 11.1%	MS Register vs. MS Outpatients NS MS Register vs. General Population p=<.0001 MS Outpatients vs. General Population NS
Comments Neutral	5, 83%	549, 59.8%	24, 70.5%	85, 52.4%	
Comments Positive	-	80, 8.7%	2, 5%	25, 15.4%	
Missing	6	41	16	54	

*The HCP group was not compared due to low numbers.

NS=Not significant

The MS Register cohort was associated with more negative feedback

When the cohorts were compared to the MS Register, there was a statistically significant difference between the negative commentary of the MS Register cohort with 289/918 (31.4%) versus the General Population with 18/182 (11.1%) (Pearson's 2x2 χ^2 p=<.0001). Those as part of the MS Register were more likely to provide negative commentary about the film. There was no difference seen between the MS Outpatients and MS Register cohorts nor the MS Outpatients and General Population. See table 17.

The film concepts were less understood by those who were negative and separately, those who were degree educated

All four concepts were less understood by those who commented about the film negatively when compared to those who were neutral/positive: car (p=<0.0001), tree (p=<0.0001), pollution (p=<0.0001), engine (p=<0.0001) (all results 2x2 χ^2 2-tailed Fishers Test).

Behavioural traits associated with education in an independent cohort

To investigate what attributes may be present in a degree-educated audience, the MS-DOUBT cohort (chapter 3) was reviewed again to determine if additional characteristics were present in an independent dataset (chapter 3). A multivariate analysis was performed looking at all personality and behavioural covariates (as recorded by the TEIQue questionnaire) to determine if any associations could be made with higher levels of education. Three variables were associated with degree-level education (n=55): emotional regulation (B, [CI 95% lower, upper], p-value: -.302, [-.566, -.037], .026) empathy (.231, [.004, .458, .046) and adaptability (.341, [.012, .671], .043). Emotional regulation is the capacity of a person to regulate emotions, which involves staying calm if upset by a situation. Empathy is the capacity to take onboard the viewpoints and feelings of others. Adaptability is how well a person deals with change. This demonstrated that those with degree-level education were associated with lower emotional regulation, higher empathy and higher adaptability (Petrides, 2009).

Self-perceived understanding was also measured within the film commentary. Six-hundred and ten of 918 (66.4%) directly referenced the themes highlighted in the 'Understanding – importance of action (Positive/Neutral)' – see table 18. However, 148/918 (16.1%) highlighted that self-perceived understanding was achieved through the additional context/explanation that the website provided in addition to the film.

4.15 MS Register - Film Commentary

A number of themes emerged from the film commentary both positive and negative – the results are summarised in Table 18. The main theme understood (in terms of frequency) was self-perceived understanding of the film's primary message – variations on action and early intervention, as demonstrated by the sub-themes and codes.

The value of the research was also acknowledged ('helpful to newly diagnosed'. 'important message', 'educational'). Stylistically, there were positives ('good analogy', 'relatable', 'well produced animation') and negatives ('music presents a rose-tinted view of MS', 'too abstract', 'crayon effect interferes with message'). Some pwMS transmitted their own experience to the film's message for eg. 'Postcode lottery for treatment', 'Needs shown to GPs', 'Places blame on the person with MS'. In terms of attitude and feeling towards the film, there was some evidence of visceral response positively expressed (reflective, powerful, poignant) and negatively interpreted (patronising, depressing, upsetting).

Table 18: MS Register Cohort – Film Commentary themes

Themes	Subthemes	Codes
Self-perceived understanding – importance of action (Positive/Neutral)	**Early intervention**	Early intervention is good, early diagnosis, seek help early, early treatment, time is key, act quickly, address symptoms immediately, don't leave small problems as they get bigger, don't delay treatment
	Prevent Deterioration	Prevent breakdown, longer symptoms are ignored – harder to treat, early treatment slows progression, prevent deterioration
	Body Deterioration	Things break, Symptoms of MS deteriorate over time, problems can deteriorate
	Importance of Signs	Recognise symptoms early, look for small signs, don't ignore changes
	Self-care	Look after yourself, aware of self, if you neglect body – problems will arise, listen to body, get body checked regularly, be proactive about treatment, take health seriously
	Representative of MS	MS can manifest in different ways, Demonstrates effects of ignoring MS, conveys sensory reality of living with MS, Chemicals damage CNS and the body stops working, After attacking immune system, MS effects whole body, Immune system breaks, How MS affects someone, late presentation can lead to irreversible damage
	Symptoms are insipid	Damage can be internal, Disability progression may be unnoticeable at early stages, illness can be invisible

Self-perceived Understanding (Positive)	**Value of research**	Good message, Educational, Educates people about MS, Important film, Important Message, Illustrated how different choices could be made, Helpful to newly diagnosed patients, Understood
Self-perceived Understanding (Negative)	**Lack of self-perceived understanding**	Unclear, confusing, Unclear aspects, Tree represents seasons passing
	Needs context	Commentary needed, Explanations needed, Supplementary information needed
Stylistic	**Style (Positive)**	Excellent, good, Lovely video, Good choice of person, Good analogy, Interesting, Good visual of MS, Clear Direction of Film, Beautiful film, Well produced animation, Well presented, relatable
	Style (Negative)	Too abstract, Too metaphorical to convey message, Unclear metaphors, Lost message, Complex analogy, Crayon effect interferes with message, Needs to be harder hitting, Music suggested a rose-tinted view of life, Thought differences would be seen in the woman
Visceral	**Visceral (Positive)**	Meaningful, deep, thought-provoking, reflective, powerful, poignant, Invaluable, Beautiful film, Very enlightening, Food for thought
	Visceral (Negative)	Patronising, Condescending, Doom, Depressing, Upsetting, Bleak, Pessimism, Troublesome, MS is grim, Negative
Personal Experience/Environment	**Personal Experience/Environment**	Should be shown to GPs, Postcode lottery for treatment, Places blame on the person with MS.

4.16 MS Register – General Commentary

The general commentary offered additional insight into the personal experience with early intervention as the focus. Consistent with this, the majority of comments were variations on early intervention (see table 19) but this time more context was given in relation to the healthcare system (as a main theme). For this reason, the codes recorded in table 19 have been extended to give greater insight. One expression of early intervention was the importance of a timely diagnosis and investigations which would enable early treatment access. Connected to this, there were recommendations to educate GPs (as primary care referrers), MS nurses and other HCPs, about MS and the importance of early action in order to give people the best possible chance of early treatment.

Early treatment was acknowledged but others were more cynical. This view reflected personal experience for e.g. becoming more ill as a consequence of taking treatment; concerns about side effects; lacking understanding of the disease itself; making a decision when well or asymptomatic; the fact that there is not a 'gold standard' one-size-fits-all treatment; and some concerns about the biggest beneficiaries of the process including drug companies/shareholders. Connected to this, some people expressed concerns about accessing treatment due to prescribing criteria as well as where they lived, despite a willingness to take treatment. Concern was also expressed about the beliefs of the HCPs themselves: their own level of education and whether they favoured a 'wait and see' approach indicating that their position on treatment would influence whether or not they would prescribe.

Table 19: MS Register Cohort - General Commentary themes

Separate comments attributed to different individuals within each cell under the 'codes' heading is indicated by the semi-colon between comments.

Themes	Sub-themes	Codes	Number
Healthcare system	**Early diagnosis pivotal; diagnostic tools**	Early diagnosis has to occur before early treatment; More diagnosis tools needed; wish had diagnosis sooner-it may have helped lessen my problems now; just as important as early treatment is early diagnosis; it took over 14 months to diagnose by which time my symptoms had increased; I think that the greater problem is getting quickly to the correct diagnosis and a position in which treatment is recommended. For me this took 6 years and 4 relapses.	38
	Delays being seen; investigations should be faster; discharged from care; symptoms not always obvious/diagnosis complex	I was left without appointments for 10 years; I lost valuable time; long wait for scans and tests; Want another DMT but NHS and poor accessing to staff preventing it; It's lack of access that's the issue, not a lack of willingness on behalf of the patient; the NHS needs to act faster; delay in referrals to specialist services; I feel strongly I am being left to fend for myself with no support from NHS; occasional appts with MS nurse; discharged from care; months can be lost because of admin and ineffective MS nurses; When I was diagnosed after a few years of symptoms it then took about two years to get an appointment with a consultant who could start me on [DMTs]; Whilst early treatment is good, the early symptoms are not always obvious so often diagnosis comes when there is already a fair amount of damage or progression.	59
	Educate HCPs, GPs; Communication (positive and negative); role preference	HCPs need to be clear in encouraging early adoption of DMTs; MS nurses must inform patients; my message to people who think that it won't happen to them because they still feel well, is, it probably will, so don't wait until it's too late; standard response to 'watch and wait'; knowledge and communication poor in past; Neurologists play 'Russian roulette'; HCPs not up-to-date with treatment options; Poor advice from HCPs; been told what I've perceived an issue isn't an issue; appalled and shocked at abrupt manner [consultant]; Doctor was rude and abrupt; was not given opportunity of	69

		comprehensive conversation with consultant; Perhaps providing regular short update courses for GPs, who cannot be expected to be specialists in all areas and early on in their careers are building up knowledge of a huge range of conditions, might help; As soon as MS was diagnosed I was put on Rebif injections 3 times a week. There was no question or discussion. I just got on with it. However I did have a very supportive MS nurse who congratulated me on the way I was feeling and how I responded to the news of MS; It is owed to patients to educate them regarding risks/reward/utility of early intervention with an effective DMT. A repeated problem is the newly [diagnosed] patients often feeling that they are being required to choose an appropriate medication and do their own research; I was given a choice of treatments fairly soon after being diagnosed, with an explanation of the benefits and side effects of each treatment. All of the information was good and I would still like to have been given a choice but I would of preferred it if my neurologist had told me which one he thought would suit me best.	
Treatment issues	**Early treatment important**	Earlier treatment started, better the outcome; I'm in favour of early treatment; once the damage is done it is unlikely to be repairable; remissions can give sense of non-urgency; everyone should be offered early treatment; strong agree with early treatment; early intervention vital; [treatment] kept me working and driving; this is the knowledge we have now; starting treatment gave me back control; early treatment should be encouraged; I think everyone should be given the option to have aggressive treatment as soon as they are diagnosed.	222
	Early treatment intervention (unsure);	Become more ill with each attempt at treatment; concerned about side effects; found it difficult to make decision about early treatment as didn't understand disease; difficult if one is feeling reasonably well; I was really well and the time and couldn't contemplate having something that would make me ill; not a one-size-fits-all treatment; it is not for everyone; too quick to jump into strong meds whose side effects will be worse than the MS itself; the biggest beneficiaries of this process are drug companies/shareholders.	38

	Side effects; risk factors; asymptomatic; no gold standard treatment; administration & efficacy	No comment in film about side effects and less than 50% success rate of treatments; so many choices of DMT available-no definite way of choosing best option; I must confess to putting treatment off as I found it scary/confusing; treatment means regular follow-up; could not manage side effects and look after daughter; taking a drug when you feel well is a difficult choice to make; chose treatment observing disability in others; I have never had a disabling relapse and currently very well. I would need to be convinced of the benefits before I accepted treatment; I worry about side effects and how they might affect other areas of my life; Recognise early treatment is important even without symptoms; So many choices of DMT available and no definite way of choosing the best option; Worried about the side effects of the drugs; Early treatment also needs to account the type of treatment administered. I feel like there is an over reliance on older medications that don't have the same efficacy as some of the newer treatments that have been developed.	82
	Eligibility, interpreting relapses, unable to access treatment; comorbidities; postcode lottery; progressive disease; diagnosed in different era; funding issues	Waiting for two or more relapses in a 12 month period before qualifying for treatment is not great physically or mentally for a newly diagnosed person; difficult to persuade neurologist to prescribe; I have opted to start [treatment] but that was the best my [neurologist] could offer because I have so many other complicated health conditions; treatment eligibility significant; postcode lottery; more clarity needed on what a relapse is; hard to know what relapse is-can be barrier to treatment; nothing for PPMS; In UK not eligible for most treatment; not seriously deteriorated…because of this discharged from care; treatments offered and the neurologists are not there; was told early treatment not available in UK on the NHS; Too late for me; depends if your C.C.G will fund it; I'm struggling to access treatments; Recognised treatments such as HSCT that are proven to halt MS in a high percentage of patients is basically impossible to get in the UK. The criteria is flawed and far too narrow. UK treatment seems to be focused on managing symptoms once its too late and MS has progressed to disability; I wanted to start treatment as soon as I was diagnosed but I didn't qualify.	155

Education	**Lack of knowledge; Informed choice**	Knowledge is key; more education is needed about benefits of early treatment; information helped me to decide what to do; Need to do your homework-take the time; left to work it out for yourself; I had no knowledge, understanding and the importance it was to start DMT [when had the chance]; I have never been offered DMTs to help with my MS – should I have been?; "Had no idea treatments could radically improve my likely outcome. Had I known I would have chosen a different path; I was never told that early intervention could help me; [Re: treatment] It must be informed choice. A patient being involved in their own care plan enables them to take a more active role in their own care; It's scary once you are diagnosed but you need to educate yourself and take control; More clarity needed to confirm when or whether a relapse has occurred and how it should be recorded; When I was first diagnosed I didn't understand the disease or how the treatments would help me at the early stage.	50
	HCP held beliefs; education; 'wait and see' approach favoured	Neurologist not proactive; my consultant encouraged me to do nothing for the first 3 years; consultant decided against as I was well; MS nurse told me I should not be in a hurry; when diagnosed there was a wait and see approach; it is not usually offered; early treatment is not pursued by my consultant or MS nurse; My neurologist is more concerned about his budgets and his risks, not mine; [DMT] ws not encouraged by my first neurologist who I saw annually from 2005 – 2013; I wasn't given treatment until my symptoms progressed because I was reliant on the advice of the consultant who is the professional. My life could have been very different if treatment had started earlier; If the medical world were really serious about treating and finding a cure for MS they should immediately stop the 'wait and see' policy that continues to exist.	29
Miscellaneous	**Unanswered questions-treatment approach factoring: different MS type, disease diagnosis and**	Is early treatment right for everybody? Why are DMTs not offered to people with RRMS for a while and still having relapses? Is it the same for RRMS and PPMS? What are the likely outcomes of long-term MS? When does confirmation of the disease occur? At what stage does treatment start? I've had MS nearly a decade, with early treatment in mind can any damage in the early years be repaired?; What about psychological help/intervention?;	13

	timepoint, postcode lottery	Shouldn't everyone have the option of early treatment? I have not. Is this a question of postcode?.	
	Lifestyle	Lifestyle changes should be put in place in parallel: Stop smoking, vitamin D, diet, stress reduction; not nearly enough emphasis on lifestyle changes; look to reduce stress & concentrate on mindfulness; decided against meds and to go down the non-dairy diet line; DMTs alongside a holistic approach; neurophysio, occupational therapy and counselling; physiotherapy, hydrotherapy, reflexology; losing weight…faith; positive attitude; What about psychological help/intervention?.	28
	Denial, ignorance of disease	People want to continue with normality…almost ignore MS in their lives; The idea that it won't happen to you (deterioration); some in denial that it will get better; challenge to communicate importance of early treatment in MS as I suspect reaction is denial; I decided not to Google and worry myself…I was completely ignorant; I think it's hard as your mind is in shock, there is so much to come to terms with and not a lot of help out there to do so (back in 2004).	14
	Identity: confidence, independence	Total loss of confidence after MS diagnosis; The hardest part of my MS is having to ask family members and friends to do things for you when you [were] so independent and able to do anything you wanted.	3
	Different approach: emphasis on pros over cons of treatment; trauma of diagnosis; involvement of significant others	[Re: early treatment] Encouragement rather than fear should be mantra; It needs to be made clear that interventions include things like Neurophysio, Occupational Therapy and Counselling; When someone is told they have MS, I don't think they should be expected to retain much information, there should be another appointment…3 months later and then after another 3 months. I know this can't be maintained…just at first there is a lot of information to assimilate; It is difficult to make a decision about treatment when you don't know how the disease is going to affect you. Everyone is different and may be taking a drug when progression may have been very slow; [on treatment] It's a big life decision and must involve loved ones and carers	19

	Anger, frustration	I am very bitter that I wasn't offered this [treatment]; No desire to find treatment for PPMS. Yes I am bitter and angry. Damn angry! I'm existing not living.	23
	Regret	Five years after diagnosis that [consultant] started me on [DMTs]…wish it could have been sooner; I am sure that if I had been diagnosed and treated early I could have halted the progression of the disease; The importance of early treatment needs to be demonstrated more. It had been pushed on to me more my life would be different and I wouldn't have taken two years to agree; My MS has deteriorated and in hindsight I wish I would have commenced treatment when I was first diagnosed; I have progression which limits my mobility now and I wish I could have had interferon when I asked for it in 2001; I wish that I had been made aware of the help and medication when first diagnosed. Sadly this has left me disabled now.	50
	Pregnancy	I want to start a family and therefore feel my current option is to start a lower effective treatment… there is a huge lack of support for women in my situation.	9
	Other: film-related, personal commentary unlreated to the question	In 1994 I had double vision I went into hospital and had a treatment for steroids, it did not cure the double vision but they did help. I still have it today …; Film was effective and none frightening in my opinion	36

A number of miscellaneous themes emerged that did not fit with the main themes but are included here for additional insight. These included unanswered questions in 13/499 (3%) indicating that some pwMS can't find answers elsewhere for e.g. Is early treatment right for everybody?'; 'What are the likely outcomes of long-term MS?'; 'When does confirmation of the disease occur?'; 'Can any damage in the early years be repaired?'

The importance of early intervention was acknowledged by 222/499 (44%) with a further 82/499 (16%) mentioning treatment factors including the risks involved and side effects. Sixty-six of 499 (13%) would have considered early intervention had it been offered to them and 30/499 (6%) were unaware of the importance of early intervention. Issues accessing treatment were acknowledged by 155/499 (31%). Regret was interpreted in 50/499 (10%) with deterioration cited as a consequence of not starting treatment sooner among other reasons.

The importance of early diagnosis and diagnostic tools that contribute to a timely diagnosis were referenced by 38/499 (8%). Delays being seen by HCPs, the need for quicker investigations and related issues were raised by 59/499 (12%).

Lifestyle choices beyond treatment were deemed important in the context that great emphasis is placed on medicinal interventions. Examples included: Lifestyle changes should be put in place in parallel: Stop smoking, vitamin D, diet, stress reduction; look to reduce stress & concentrate on mindfulness; decided against meds and to go down the non-dairy diet line; DMTs alongside a holistic approach; occupational therapy and counselling; physiotherapy, hydrotherapy, reflexology; losing weight, faith; positive attitude. The 'lifestyle' theme was referenced by 28/499 (6%).

See table 19 for a more comprehensive interpretation of the themes found and the reasons cited by study participants.

Car remains a popular concept when themes are taken away

Wordclouds were used to visualise the commentary data to determine if any key concepts remained or emerged when the themes were removed from analysis (figure 25). When the themes were taken away in order of the themes identified in table 18; firstly, with all themes included (image 1), minus self-perceived understanding (image 2); next minus self-perceived understanding and stylistic themes (image 3) and finally minus self-perceived understanding, stylistic and visceral themes, the car concept was consistently referenced. This reinforces the findings in table 12 which sees car as the most understood concept.

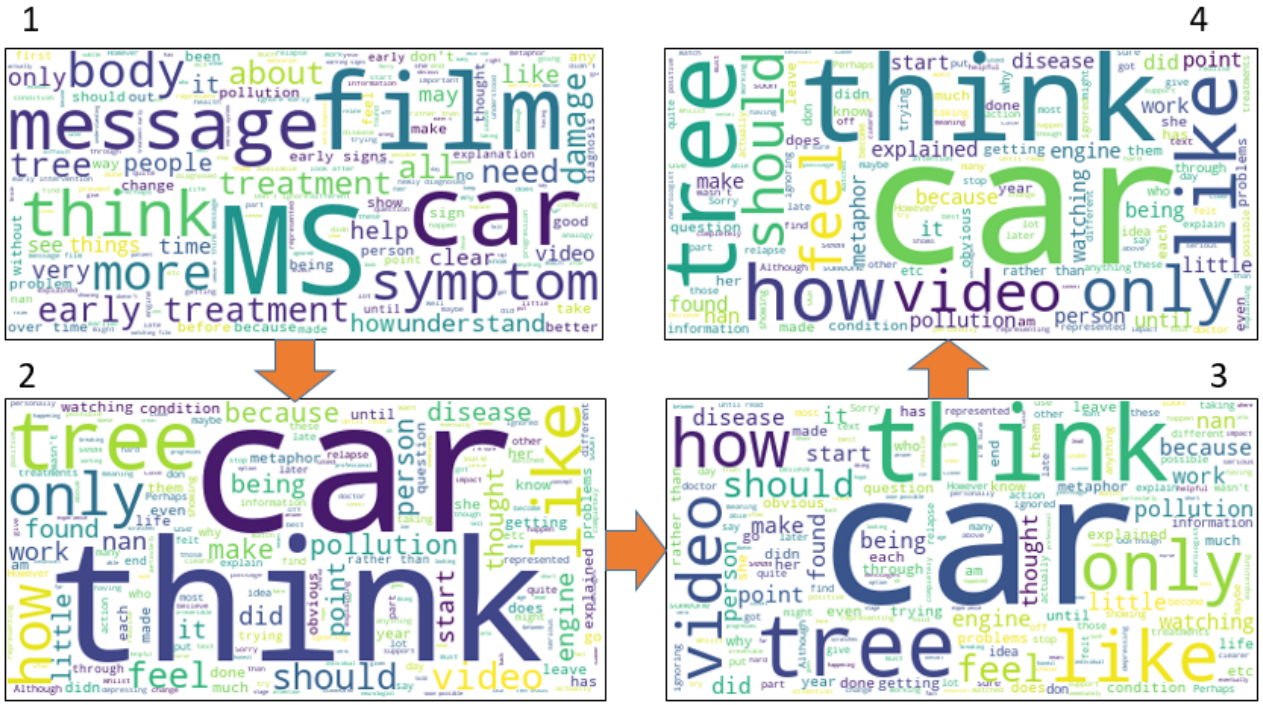

Figure 25: 'Word clouds ordered 1-4 show film commentary with themes removed in stages'

Consistent with themes presented in table 18 beginning with all commentary, represented at each stage are words that patients used with the most frequently referenced words represented by larger font size. On average, 'car' was the most frequently cited word.

4.17 General Population and MS Outpatients – results

4.17.1 Demographics

Demographical data was not recorded for the General and MS Outpatients populations as responses were anonymised, nor were the numbers large enough to provide YouTube/Google analysis pertaining to location, gender and age.

4.17.2 Access

The website incorporating the film was accessed by both populations between 12th July 2019 – 4th October 2019. Within the General population, 182 responded to the questionnaire and confirmed a non-MS disease status. Of this number, 148 (81.3%) completed the four concept questions on self-perceived film understanding and their response was therefore usable.

Of the MS Outpatients population, 50 responded and confirmed an MS status (MS type was not recorded). Of these, 42/50 (84%) answered the four concept questions on self-perceived film understanding and were therefore usable. Patients were approached by the thesis author in outpatient clinics at Charing Cross and St Mary's Hospitals (Imperial College Healthcare NHS Trust). See figure 26 for flowchart of study participants by population.

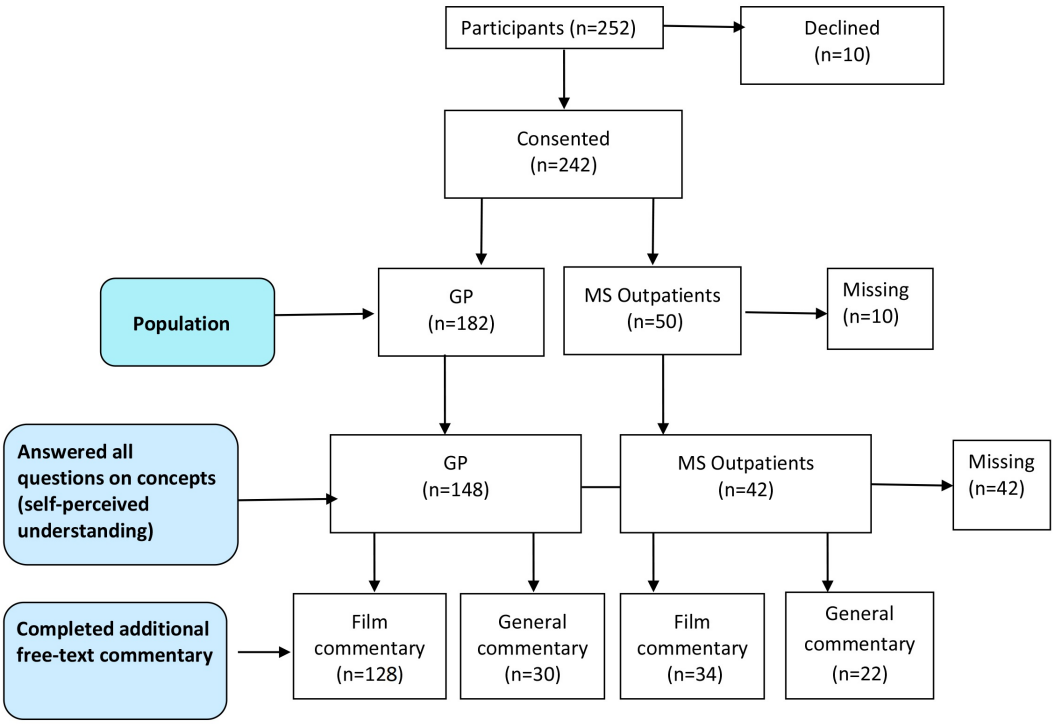

Figure 26: Flowchart of General Population and MS Outpatients cohorts

4.17.3 Self-Perceived Understanding

Within the General Population, the car was the most understood concept (96%), followed by the car engine (95%) and pollution and tree (both 95%). All four film concepts were understood by 136/148 (91.9%) compared to 3/148 (2.0%) who understood none of the concepts.

Within the MS Outpatients population, the car was the most understood concept (88%) followed by the car engine, pollution and tree (all 79%). All four concepts were understood by 29/42 (69%) compared to 4/42 (9.5%) who understood none of the concepts. See table 12.

The General Population has the highest understanding of the film concepts

When the cohorts were compared by concept understanding (total (4) versus 0-3 some or no understanding), there was a significant difference seen between the MS Register and General Population cohorts (Pearson's 2x2 χ^2 p=0.000) and the MS Outpatients cohort and the General Population cohort (Pearson's 2x2 χ^2 p=0.000). This result shows that higher understanding is associated with the General Population cohort. No difference was seen between the MS cohorts.

4.17.4 Engagement

Average viewer duration in the General and MS Outpatients populations was 2 minutes: 35 seconds equivalent to 94.5% as measured using YouTube analytics. One-hundred and forty-three views were recorded of which 132 were unique. Therefore 132/191 resulted in a 62% retention rate. A 50% retention was expected so this result exceeded the research aim of 50% (p=<.000, Binomial test). The MS Outpatients cohort was incorporated into this measurement and it was not possible to stratify viewer duration by subcohort due to the anonymous nature of the research.

4.18 General Population & MS Outpatient Cohorts – film commentary

The themes in table 20 represent the film commentary of the General Population cohort. The underlined themes are those that are attributed to the MS Outpatients cohort. The data is presented together here to indicate that there was generally consensus across all themes with the exception of one: 'personal experience/environment', which was a topic relevant only to the MS subcohort.

Table 20: General Population and MS Outpatient Cohorts – Film Commentary themes

The General Population cohort contained a subcohort of pwMS from outpatient clinics. The MS Outpatients' codes are indicated within the table as underlined to indicate that there was crossover to the themes generated by the General Population.

Themes	Sub-themes	Codes
Self-Perceived Understanding – importance of action	**Early intervention**	Early intervention is good, early diagnosis, seek help early, early treatment, time is key, act quickly, address symptoms immediately, benefits of early treatment, importance of early action, don't delay treatment, improved outcomes with early treatment, treat early; early intervention is best
	Body deterioration	MS sufferers deteriorate fast, body deterioration, body breakdown, Things break, Look after car before it breaks, symptoms of MS deteriorate over time, problems can deteriorate
	Prevent deterioration	Prevent breakdown, the longer you ignore symptoms the harder to treat, early treatment slows progression, slow deterioration, prevent serious issues, don't ignore signs, take action
	Represents MS	Look for changes in body, know early symptoms, note early signs, note obvious signs, MS can manifest in different ways, demonstrates effects of ignoring MS, Progression over time is ignored, conveys sensory reality of living with MS, Chemicals damage CNS and the body stops working, effects of MS on body
	Invisible symptoms	Symptoms are insipid, damage can be internal, disability progression may be unnoticeable at early stages, illness can be

		invisible, changes in body can be subtle
Self-Perceived Understanding (Positive)	**Understood film**	Understood, understanding
	Value of research	Good message, educational, informative, educate people about MS, important film, important message, illustrated how different choices could be made, helpful to newly diagnosed patients
Self-Perceived Understanding (Negative)	**Didn't understand film**	Lack of understanding, unclear, confusing, unclear aspects
	Context	Commentary needed, explanations needed, needs context, supplementary information needed
	Value of research	Message doesn't resonate with self, should compare to someone who has checks, needs to show change with early intervention, not useful for newly diagnosed, doesn't aid decision-making, helpful to newly diagnosed
	Lack of understanding	Environmental impact, tree represents seasons passing, lack of understanding
Stylistic (Positive)	**Style (positive)**	Excellent, good, lovely video, good choice of person, good analogy, interesting, good visual of MS, clear direction of film, beautiful film, well produced animation, good analogy of MS, well presented, understood car analogy, relatable, powerful visual metaphors, simple broken engine analogy was clear
Stylistic (Negative)	**Style (negative)**	Negative, too vacuous, weak associations, too abstract, too metaphorical to convey message, unclear metaphors, complex analogy, lost message, crayon effect interferes with message, needs to be harder hitting, music

		suggested a rose-tinted view of life, thought differences would be seen in the woman, animation made things difficult
Visceral	**Visceral (positive)**	Powerful, positive, emotive
	Visceral (negative)	Patronising, upsetting, depressing, doom and gloom, scary, pessimistic view of MS
Personal Experience/Environment	**Personal Experience/Environment**	System offers cheap drugs first, In denial when diagnosed, MS difficult to diagnose, left on own to make decisions; told by nurse MS can't kill you, told by nurse don't try to fight MS; talk to other patients, medication is doctor's choice without discussion
Miscellaneous	**Miscellaneous**	People with MS are normal members of society, people with MS have a special problem, where to get help?

4.19 Discussion

This chapter describes a film developed to convey the importance of early intervention in MS. The film was evaluated and succeeded in a primary research aim, achieving a high level of self-perceived understanding - as measured by the four concepts - in the total population studied. The car was the most successful concept, understood by 90% of the combined population. The car also featured prominently in the word clouds. The high self-perceived understanding reinforces the power of the car as a device that can be linked to other phenomena - in this case to a person's body.

Metaphor has been used sparingly in MS films previously, most notably in the work by the Shift.MS group with films including 'Gallop' which shows a white horse within a film narrative to demonstrate courage in response to an MS diagnosis (John, 2012). Concealed symptoms have been explored in another Shift.MS film titled 'Hidden' showing sinister, ghostly characters, manipulating people's bodies (Tobias, 2018). Both films are ten minutes in length and aims are to elicit conversations in people and to encourage engagement.

The MS film presented in this chapter was less than three minutes in length and was accessed by a range of mediums including mobile phones, showing that people access healthcare information and complete research on the move. This film featured no direct reference to MS and employed only visuals and music without on-screen words, dialogue or diagrams. To the thesis author's knowledge, the combination of these components in film-form has never been presented previously in MS.

An aim of the film was to target pwMS newly diagnosed and treatment naïve as this group would benefit most from the film's message of early intervention. To help determine if the film succeeded in responding to these aims, the population was stratified by disease duration: a newly diagnosed group (0-3 years) and those diagnosed $\geq$4 years. There was a high proportion of people not on treatment (80%) in the newly diagnosed group and this was significantly different to those diagnosed longer. In addition, the newly diagnosed group were significantly younger (20-39), consistent with when most people develop MS (Dimitrov and Turner, 2014).

When the disease duration subgroups were analysed more closely, a more progressive, older population of longer disease duration commented more negatively. When wordclouds were used to isolate the most frequently cited words within each subgroup, it was evident that there were differences in commentary. Those in the visceral-negative longer disease duration group challenged the film's message and whether it would be effective in those newly diagnosed.

Irrespective of response to the film, a high level of self-perceived understanding was still achieved in both disease duration subgroups. This suggests that the film was effective regardless of how it was perceived emotionally, and raises questions as to whether films that unsettle have in fact served their purpose if they lead to understanding. Indeed, there is opinion that emotional response (both negative and positive) in film benefits learning (Jones, 2016a). Public information films have been known to unsettle but they are memorable for it (Rogers, 2010). When the visceral-negative response was removed, it was evident that there were similarities between the disease duration subgroups with very similar wordclouds confirming that the film's message about early intervention and notably the importance of the diagnosis stage, came through.

Within the MS Register cohort, those with the lowest levels of education had the highest self-perceived understanding of the film's central concepts. This is an important finding as those with less education have been found to be less likely to seek out health information with decreased confidence in their ability to access health information (Richardson et al., 2012). Where this film did succeed was in

accessing this group. The message was understood in the MS Register cohort, further supported by the free text 'film commentary' with 66.4% acknowledging early intervention in addition to the high self-perceived concept understanding. However, it should be emphasised that the evaluation of each concept was binary (yes/no), hence actual understanding would need to be evaluated with additional measures.

What was less clear, was why pwMS as part of the MS Register educated to degree level or post-graduate level were more likely to be negative about the film. This was supported with the following commentary:

> *"I must be very stupid (don't actually think that's the case as I have an M.A. from Oxford!) as I missed the point completely….maybe I'm overthinking"*

This commentary suggests that there may be additional characteristics associated with a higher education perceived by a person and which may help explain a more critical stance. An expression of this is social identity.

A person's highest qualification is the most frequently used indicator of socioeconomic status (Winkleby et al., 1992). A more positive social identity has been attributed to higher education (Easterbrook, 2013). In addition, people with a higher education are more likely to engage with health and self-motivated activities (Daly et al., 2002).

It is possible that a positive social identity could be challenged by the film – particularly in those who had a visceral-negative response. Negative and negative-visceral responses to the film could be better interpreted once people's personal circumstances were taken into consideration. For example, the message within the film pointed to early treatment and the results of non-action, but pwMS challenged this, highlighting that it was not easy to achieve for the points raised referencing eligibility, despite a willingness on their part to try treatment. This also helps explain why some pwMS felt the film blamed them or that it patronised them.

This theory is partly supported by the results of the independent dataset. The MS-DOUBT cohort was reviewed again and three variables were associated with degree-level education: lower emotional regulation, higher empathy and higher adaptability. As adaptability can be interpreted as how well a person can deal with change, then the film could be interpreted as challenging a person's ability to do this, hence the negative response. There were some concerns that the film might upset people, which would help explain the role of higher empathy and the lower emotional regulation in the educated group could help explain the visceral-negative response.

The negative response could possibly be attributed to a pseudobulbar affect that has been said to affect between 10%-46% of the MS population. This effect is caused by damage to the CNS which can impact emotional response and which is not always appropriate to the situation (MS_Trust, 2018d). Another reason could be the anonymity offered by the Internet whereby people may be more candid in their opinion. This phenomenon has been referred to as the 'online disinhibition effect'

where some people are more inclined to self-disclose or act with more intensity than they otherwise would in-person when they express their opinion over the Internet (Suler, 2004). This could also help explain why the subgroup of MS patients approached by the thesis author in the outpatient setting were less visceral in their negative commentary, as they had been "identified" even though their responses remained anonymous.

It is also feasible that the film triggered an emotional response in some pwMS because it reminded them of their own situation. Taking onboard people's frustrations with the healthcare system manifested as too much time to be diagnosed and to be seen for investigations leading to treatment commencement. There was also confusion as to what a relapse represents and there is evidence that interpretation of relapses can be problematic (Asano et al., 2015). Relapses were singled out because they are often referenced as a determinant for accessing certain treatments. Ultimately, it is up to the neurologist to interpret the patient experience of the relapse so how it is communicated is key. PwMS felt it contradictory to suggest early treatment intervention is recommended to prevent further damage when damage has to be proven before treatment is prescribed. Some people were discharged from care with one respondent commenting that they were 'too well'.

There was some acknowledgement of not realising the importance of early treatment in MS or having never been offered treatment in the first place or having had it sufficiently discussed. Some pwMS would have done something about their healthcare situation sooner - had they known, suggesting that DR was present.

However, this intention was further complicated by the era in which they were diagnosed and problems accessing treatment.

It could be that the HCP could not prescribe treatment due to ineligibility but some pwMS were doubtful, questioning other reasons behind being denied access to treatment. Reasons for this included a 'wait and see' approach favoured by some consultants and nurses when evidence suggested otherwise (implying a lack of education), as well as a reluctance to prescribe due to costing implications and being denied treatment due to location in the country ('postcode lottery').

It was therefore recommended by pwMS that more education needed to be imparted to patients on recognising the signs of what constitutes a relapse so the HCP could interpret this more easily. In terms of speeding up the system, people recommended better education about MS for GPs referring and more emphasis on the importance of early treatment intervention.

Why the educated audience did not like the concepts is an interesting finding and raises questions about how healthcare information must consider different audiences when presenting risk. Some of the stylistic feedback pointed to the fact that whilst early intervention was supported in some people who recorded negative feedback, it was the style of presentation and the concepts portrayed that they did not like. It is likely that pwMS will have seen other presentations of MS as part of the lived experience for comparison and developed a viewpoint based upon this where as those from the General Population would not have had the same level of reference.

Of particular interest, the General Population had the highest self-perceived understanding, suggesting that the message was presented in a way that appealed to a universal audience, although this would need to be replicated in a larger population with measurable demographics.

There are some limitations to this study. Although the majority of aims were met, it was not possible to capture the remaining measures due to the way in which the film was hosted. For example, the 'Transfers from Video' measurement was not relevant as the film was incorporated into the website. The original intention, inspired by the prototype website, was to measure how many people accessed the research from YouTube and then transferred to the website to find out more information. This number would then be compared to the number of views of the film. Connected to this, as a secondary outcome, the original intention was to record the most visited sections of the website. Due to the manner in which the website was hosted via the MS Register, this could not be captured.

In addition, the 'Time to Treat' measurement was dependent on the RCT component but this was not carried out. The numbers for the General Population were below the study aim on the basis that it was very challenging to recruit people without MS to complete the research owing perhaps to the lack of personal investment in the disease.

Demographical information was not available for the General Population and MS Outpatients due to the anonymous nature of the data, meaning no distinction could be

made between individuals using YouTube analytics and the numbers were not high enough to obtain group demographics. On reflection, group analysis could have been achieved by isolating the two groups by time period, but this was not possible due to the time constraints of the PhD. In addition, because the research was in the public domain, it was not possible to restrict user access to a time point. This could be overcome with a method for restricting access with for e.g. a password system, for the purpose of evaluation.

Additionally, no comparison could be made in terms of education to the MS Register – which proved significant in the original cohort. However, attitude (as defined by commentary) was measured across cohorts and it was found that the negative-visceral response was significant to the MS Register cohort when compared to the General Population but not to the MS Outpatients population. This suggests that there may be disease-related characteristics that trigger the emotional response and certainly the commentary appears to support this theory. A limitation of the research is the low numbers in the comparator populations and this research would need to be replicated in the future to address this.

Whether behavioural change was successfully encouraged or instigated in individuals by the film is open to interpretation in the absence of an RCT testing the intervention against a control arm represented by standard care – as was originally intended. It was not possible to achieve this due to the negative response to the film. Ethically, a decision was made not to proceed and instead to incorporate a subcohort of outpatients with MS into the General Population cohort, however this component

was not powered for this reason. The RCT proposed was powered to recruit 100 participants. Practically, an RCT with a limited target population of newly diagnosed patients would likely involve a multi-centre design and considerable resources which were not available at this time.

On some level, film effect is suggested in those who mention that they would have approached treatment sooner but this cannot be quantified as some of these people now fall outside of the treatment window or their circumstances have progressed to the stage where they are no longer treatment naïve. In summary, they are not a measurable audience.

There are further limitations with the YouTube analytics and the manner in which the film was hosted, in that the film content could not be directly linked back to the individual. For this reason, it is not known whether a portion of the population watched some or all of the film. The 'unique' views is a conservative estimate and discounts multiple users who may have watched the film on the same device. As there was a high percentage of commentary provided in 918/959 (96%) on the question directly asking about the film, it must be assumed that the actual film views were higher than the YouTube data implied, in order for these users to comment. However, the overall retention figure in the total population, as measured using the YouTube data, was still significant at 61% in the MS Register population (p=<.000) and 62% in the General Population incorporating the MS Outpatients cohort.

There was a high proportion of degree educated participants (40%) in the MS register cohort. This was higher than a UK general population (27%) taken from the 2011 census (ONS, 2013a). It is potentially a limitation of the research that the population was more highly educated than a general population. The proportion of those degree educated within the MS register cohort was however balanced in terms of numbers, to make the data sufficiently comparable within the population being studied.

In terms of positives, the film presented here had high user engagement (another primary aim) with an average duration of the film viewed in the total population of 95%. This indicated that the content was able to retain audience interest.

The film adds to a small but growing evidence base looking at the impact of film-based DAs in healthcare. This film explores risk in an abstract way to those who may not respond to established methods of communicating risk information or who may struggle with processing complex information.

The large sample size evaluating this film compares favourably with other studies. In a comprehensive review looking at 488 studies of video-based DAs, the majority featured less than 300 participants (Winston et al., 2018) where as this study executed over a six month period attracted more than 1200 participants.

Early intervention was acknowledged in a high number of participants, but there was also a number of unrelated comments and unanswered questions, which suggests that pwMS have unmet needs. The second free text question (‘general commentary’) was answered by 52% of the MS Register population and when the average word count was compared to the ‘film commentary’ question, there was a significant difference

(p=0.000) with a higher word count in the 'general commentary' subgroup. The majority of this subgroup had longer disease duration and therefore more experience to reflect upon. This result also reinforces that people were keen to share their own views and personal circumstances.

According to the MS Register, the film study presented here produced the largest free text response in the history of the MS Register and as a consequence of the free text analysis presented, in tandem with existing ways of collecting free text commentary through existing channels at the MS Register, the Clinical Director of the MS Register informed the thesis author that additional resources are being considered to help respond to the frustrations presented in the MS Register population.

4.20 Conclusion

The film evaluation succeeded in the research aims that could be measured. By offering users a free-text response and using additional variables to evaluate what may influence self-perceived understanding in the MS Register population and compared to two other populations, the mechanism by which the film made an impact was further explored.

Worthy of future exploration, was the discovery that those from the MS Register without degree-level education had greater self-perceived understanding and the General Population had the highest self-perceived understanding across cohorts. In addition, the MS Outpatients cohort also had high self-perceived understanding. For the purpose of comparison, the film was delivered in the same way across cohorts but

the way the film study was communicated initially (in-person) was unique to the MS Outpatients cohort.

These are important findings for although films and videos are seen as beneficial, they are not yet fully understood (Winston et al., 2018). We must therefore be creative in acknowledging diverse audiences, exploring the characteristics that define them and prioriting those that are relevant to the product, and ultimately find ways to pinpoint and interpret how information is absorbed differently by individuals. This will then inform products that can be tailored to specific audience's needs and how they should best be delivered.

In the following, final chapter, the results are considered in a wider context with consideration of how the results may inform future research.

4.21 Acknowledgements

The thesis author would like to acknowledge the individuals who gifted their time to participate in the film research and the UK MS Register for agreeing to host the research. In addition, MSTC for funding the film.

4.22 Contribution to work

David Wilkie: Wrote the study protocol and patient documents and obtained all regulatory permissions (ethical and internal: JRCO/information governance) in addition to grant application to the MSTC for funding the project and the UK's MS Register for hosting the project. Approached all participants in outpatient clinics and the General Population online. Scripted the film component and developed the

prototype website to host it. The thesis author performed all statistical/thematic analysis and generating of figures, tables and written content within this chapter with the exception of wordclouds.

James Cook: Production and direction of film, post-production. Figures 17-19.

Richard Nicholas: Initial car concept. Statistical advice.

Lisa Bindahnee: Legal advice/contracts between MSTC and James Cook.

Emily Miles: Acted as independent researcher ('researcher 2') on statistical analysis of film commentary.

MS Register: Adapted the website for hosting within the UK MS Register.

Sarah Knowles: Assistance generating original wordclouds (figures 23, 24), further adapted by the thesis author. Acted as independent researcher for thematic analysis of the MS Register General Commentary only.

Tim Friede: Calculated sample size numbers.

4.23 Conflicts of interest

R Nicholas and D Wilkie are funded by Multiple Sclerosis Trials Collaboration (MSTC). R Nicholas is a trustee of MSTC and Clinical Director of the UK MS Register.

Chapter 5 Discussion and Future Research

5.1 Introduction

The purpose of this chapter is to bring together the findings in order of presentation in this thesis and to review and reflect on what has been discovered. Many of the main points have already been addressed in the discussion sections of previous chapters; therefore, the aim here is to take the research, its limitations and achievements, and discuss it in a wider context and how it may be applied to the greater healthcare environment as well as addressing the potential avenues for future research.

5.2 Summary of key findings and future recommendations

The first chapter included a literature review of decision-making theory and theory-applied tools with an emphasis on healthcare and MS. It was identified that decision-making in MS is complex with a growing range of therapies with various efficacy, routes of administration and frequency, as well as risk. A person living with MS (as well as the HCP) must navigate a healthcare system where there is no agreed gold standard treatment that fits all, nor is the decision-making process fully understood.

For this reason, a number of existing measurements were investigated at different stages of the decisional process with the aim of selecting those that may be used in an MS context. Some of these instruments had already been used and validated in an MS population whilst others had not been used before to the thesis author's knowledge.

From the literature review emerged a questionnaire (chapter 2) of existing and new measurements aimed at addressing the role of treatment in decision-making in three independent populations of pwMS.

The following questions were asked:

- If DR was present referencing treatment choice (including no treatment).
- If there was DC surrounding treatment choice.
- To determine the level of influence in treatment decision-making of other parties and priority issues when deciding on treatment.
- Role preference during the clinical encounter.

From an initial population comprising attendees to an MS conference, the questionnaire was adapted two more times based upon the results from each stage incorporating pwMS on treatment and offered treatment - taken from outpatient clinics. The results were then compared as part of a cross-sectional study and showed that DC and DR vary across populations and were highest in those treatment naïve. The majority of the total population (53%) had DC.

For comparison, DC has been measured across primary care. Looking at five studies in Canada, DC ranged from 10-31% and was most associated with the male gender, living alone and aged $\geq$45 (Thompson-Leduc et al., 2016). These different findings reiterate how complex DC is and can vary at different points in the healthcare system and by decision type. The high level found in the total MS population here emphasises

the need to better understand DC in MS and how to respond to it. Clues may lie in the associations with DC confirmed in the cross-sectional study (chapter 2). Associated with DC was being on a lower potency treatment, having a passive role preference during the consultation, and being in employment.

Isolating first employment, in a large study of 11,515 pwMS, 4,469 (39%) were not in employment with 3649/4469 (82%) claiming MS was the reason. From the same study, 43% of those who stopped working did so within three years of an MS diagnosis. The report further highlights the necessity to intervene earlier to enable people to stop in work for longer (Jones, 2016b). A focus-group study aimed at employers found that 72% of the companies involved considered their work too challenging for the disabled. Additional concerns included fears of litigation and handing out compensation (Fraser et al., 2010).

Employment was a consideration for those interviewed as part of the MS-DOUBT 'offered treatment' cohort with the importance of staying in work emphasised. There was some anxiety about the perception of employers when asking for work adaptions – for example, one person interviewed was a high level teacher who has strict limitations on when they can take time away from work. Therefore it is logical when considering a treatment's route of administration (e.g. oral medication taken at home versus a hospital-based infusion) could influence a person's decision over what treatment to take, even if efficacy is lower for an oral medication. A hospital system that has the capacity to adapt to a person's individual needs is desirable but not always

possible and, indeed, this individual had frustrations with the hospital system including calls that remained unanswered on when to attend appointments and for what purpose.

The research looking into employer concerns confirms that some of the fears of pwMS are warranted. From the perspective of employers, better understanding the impact of chronic disease and disability could help take away the mystery of MS.

In a large study of 32,507 patients, looking at identifying employment-related factors in pwMS, a mean of 59% were out of work and the most frequently reported factors impacting a person's ability to work were fatigue and impairments to mobility and cognitive function (Schiavolin et al., 2013). As DC here was linked to treatment choice, there is an opportunity in future research to investigate further the association of treatment to employment. Considering the importance of work to identity, quality of life and more, it is not surprising that DC could be exacerbated by employment.

MS does not have the same exposure as other conditions in the minds of the general public and the MS Society has recently tried to address this with its largest campaign to date showing people living with the condition and the ultimate aim of raising £100 million over ten years to help fund treatments with the backing of Channel 4 and others (Schofield A, 2019). Fatigue (and its perception) was one issue highlighted in the MS-DOUBT interviews and can have a major impact on a person's ability to work. This could play a part in the nationwide campaign referenced.

Secondly, a more passive role preference was seen to be related to ethnicity but when ethnicity was taken out of a multivariate analysis, it was the passive role itself that was

associated with DC and DR. In a meta-analysis pooling US and Canadian data focused on the CPS as part of oncology decision-making, there were significant differences observed between country and gender – Canadians favouring a passive role over their US counterparts and females preferring a passive role over males ($p<.001$). Interestingly, older patients were more likely to take on a passive role (Singh et al., 2010). Comparative data does not exist linking the CPS to DC or DR in these populations.

It has been reported that there is marked difference between role preference across different territories, indicating a cultural component that may influence decision-making. In a study by Giordano et al (2008), the CPS was used to determine the role preference of 140 Italians with MS. Overall, a collaborative role was preferred by the majority (61%), followed by passive (33%) and only 6% preferring an active role (Giordano et al., 2008). This contrasted greatly with a German study of 219 MS patients, again utilising CPS, that showed 79% preferred an active role (Heesen et al., 2004). Building on this, the AutoMS project was setup to assess role preference across six European countries with preliminary data supporting the aforementioned German preference for an active role, whilst Eastern Europeans (eg. Serbia and Estonia) appeared to be more closely aligned to Italy (Sutton, 1998).

Thirdly, there was an association with lower DC and DR in those on higher potency treatment. It is less clear why higher potency treatment reduced DC as it can come with higher risk. However, an inference is that treatment that works more effectively can visibly reduce the impact of the disease and improve adherence (Wilski et al.,

2019). Having a higher efficacy treatment could also give the patient a feeling of empowerment that they are hitting their disease hard. Efficacy emerged as a key issue for people considering therapy in the cross-sectional study so this may explain the association.

The MS-DOUBT study presented in chapter 3 was more expansive and in addition to the areas reviewed as part of the first two phases ('MS conference attendees; 'On treatment' cohorts) looked additionally at personality, knowledge, depression, anxiety, lifestyle, engagement and the role of the consultation in treatment decision-making.

Firstly, a surprising outcome was that of the personality facets. All facets apart from adaptability, were in the normal range offering no real insight. Lower scorers on the adaptability scale tend to be change-resistent. They can be more inflexible and have fixed ideas and views (Petrides, 2009), (Thomas_International, 2011). How this trait manifests in real world terms is unclear – it could potentially delay a person starting or changing treatments but more research is needed and the TEIQue results here would need to be replicated in a larger MS population before any definitive conclusions could be made.

As the TEIQue has proven to be consistent over time (Pérez et al., 2005), the questionnaire was not repeated at follow-up for this reason. One study looked at personality in MS and found that so-called 'personality D' disorders were significant in the MS population studied, indicating a tendancy to express greater neuroticism and social discomfort and lower extraversion (Denollet et al., 1996) (Strober, 2017).

These areas were not studied here but could be incorporated into future research to determine if any associations could be made to role preference in particular.

The additional measurements as part of the MS-DOUBT questionnaires allowed for a more comprehensive evaluation of the determinants of DC. It was found that the consultation itself was significant in resolving DC. In addition, what components of the consultation that mattered most to the patient were highlighted in consideration of symptoms, being listened to, treated with care and concern and feeling their problems were taken seriously by the HCP.

The importance of the face-to-face consultation was reinforced by the result showing successful SDM reduced DC in the MS-DOUBT study. SDM has substantial support from respected institutions including the NHS, GMC and NICE (NHS, 2009), (DOH, 2012), (NICE, 2019), (GMC, 2013), with further support as part of an SDM collaborative, organised by NICE, with universities including Newcastle and Leeds, the Academy of Medical Royal Colleges and others (NICE, 2019) .

But implementing SDM into routine care remains challenging. Some of the challenges highlighted include the belief from clinicians that SDM is happening and that they already include patients in decisions about their healthcare. Some clinicians have said that patients don't want to be involved in making decisions (Joseph-Williams et al., 2017), although this belief is challenged by the results of the CPS tool (Chapters 2, 3), where the majority of patients favoured an active-collaborative role.

As living with MS requires navigating complex decision-making, it is important that pwMS are their own advocates with the education to inform how their health is managed in way that works for them. How HCPs and patients engage effectively is still open to interpretation as to how the ethos of SDM should best be implemented.

In response to this, the UK's Health Foundation commissioned the MAGIC (Making Good Decisions in Collaboration) programme in 2010, to determine methods for realising SDM with approved methodology. One recommendation that has come from the MAGIC programme is training to improve communication by HCPs in order to respond to the complexity of individual patient needs (Joseph-Williams et al., 2017).

A steering group comprising HCPs and patients has been setup with the aim of identifying the main hurdles to achieving better communication. Two main areas were highlighted: firstly, the differences of priority of the HCP versus the patient. An example of this disparity was the importance of time given during appointments, which was also the second finding: 68% of pwMS saw lack of time as a barrier to effective communication compared to 45% of HCPs during the consultation. From workshops between both groups emerged a checklist which pwMS can bring to consultations and which highlights their priorities for the consultation in advance to enable the HCP sufficient time to prepare (Oreja-Guevara et al., 2019).

As clinics are already time deficient and pressured, it remains to be seen how this could effectively be implemented and that an agreement between patient and HCP could

raise expectations to a level that may not be realised in the timeframe, causing more frustrations.

The MS-DOUBT findings showed a higher satisfaction rating for one consultant over others and consultants also reported a higher SDM score than the patients overall, indicating that they perceived that SDM occurred more than the patient did. However, time was not a significant finding from the 'clinical encounter' score. Could it be that time is perceived by the patient relative to how the consultation is delivered? This is an idea supported by one study that found no significant correlation between the time of consultation and the SDM performance measured (Geiger et al., 2017).

Consultations were not timed by the thesis author, but general feedback from participants gave no indication that the highest scored consultant spent any more time with patients compared to colleagues. Observing how information is delivered by different consultants is a consideration for future research although the same authors have suggested that certain physicians may be more proactive when it comes to SDM training and that those who need it most do not participate (Geiger et al., 2017). Therefore, how SDM is presented or angled to HCPs is a consideration for future research in terms of its benefits which can only happen with the support of HCPs from a range of disciplines and backgrounds.

At a macro-level, SDM is seen as desirable and measurements continue to improve in order to incorporate cross-content that is measurable from the perspectives of both the physician and patient as well as a third party role (Scholl et al., 2012), (Kasper, 2012), (Geiger et al., 2017). It has been confirmed that patients who have been

trained to be more involved in healthcare decision-making with their physician have improved outcomes including fewer reported limitations of their condition (non-MS) versus a control group (Greenfield et al., 1985). However, more robust evaluation is required of how SDM interventions are measured. An unpublished review of SDM studies in MS found only 5% of studies utilised an RCT component (Rahn, 2020). By comparison, an earlier review encompassing other conditions found 9/39 (23%) studies looking at SDM in decision-making (Shay and Lafata, 2015) indicating there is room for improvement.

The longitudinal component built into the MS-DOUBT study - when a subcohort of the same patients were followed-up one year later – enabled DC and other components to be measured across time. Those who made the treatment decision after the consultation showed improvements in DC and treatment satisfaction. By deconstructing the decisional process by prerequisites/process/outcome, this allowed variables to be isolated as part of the consultation timeframe. From this process, it was found that patient engagement (as a prerequisite) was associated with DC. This showed that those who had less confidence in their healthcare decision-making were also more likely to experience DC. DC also changed over time and it was possible to measure when the intention to treat had been made providing an average of 29 days.

Interviews were conducted to identify issues important to people in and outside of the clinical setting resulting in three prominent themes: issues within the healthcare system (the system as well as at an individual level); perception of MS and treatment-specific issues. Further scrutiny of these issues revealed ‘regret’ (as interpreted by the thesis

author) over the way diagnosis was communicated by HCPs, missed treatment opportunities due to system delays and not knowing what appointments were for to experiences of being on treatment that appeared to work and the trauma of coming off treatment due to safety concerns. Conflict over what treatment to choose was also an issue.

Patients provided some solutions as to the how the healthcare system could be improved with HCP training to improve knowledge of MS and communication of information. To a degree, HCPs are at mercy to the diagnostic tools available to them in the era in which they operate, but it is also a responsibility for all HCPs who specialise in MS to stay up-to-date with developments in order to support diagnosis and quicken the process, allowing people to access treatment without delay. It is more challenging for GPs who have to have a broad knowledge of many conditions. One approach online has been to focus on 'red flag' symptoms so GPs can quickly identify what may be a serious underlying cause from the symptoms presented and when to refer (GP Online, 2020).

As highlighted by the PAM results and DC that can change over time, there are subtleties to decision-making, hence future interventions should look at addressing specific needs at different stages of the decisional process. However, the delivery of interventions must always be considered as part of the existing healthcare environment with time, costings and other restraints.

One report highlighted that patients do not understand treatment information as part of consultations (Reen et al., 2018). Indeed the PAM result measuring patient engagement suggested that pwMS would show up to consultations but were not present mentally or felt ready enough to fully understand the information being imparted. In addition, knowledge, as measured by the RIKNO/MSKQ questionnaires, showed that improvements could be made, especially for risk interpretation.

These findings led to the development of a decisional tool in film form, created to influence or 'nudge' a person into taking action. The preventative action suggested was to elicit in the viewer the importance of early intervention and to show them the repercussions of non-action leading to future damage. The effect hypothesised was that this would lead to exploration of treatment options and ultimately to a treatment decision.

The film could be interpreted as part of a preventative medicine strategy where the aim is not to prevent the onset of a disease but damage caused by it (Clarke, 1974). Preventative strategy is part of the NHS's long-term plan with the aim of saving up to half-a-million lives (NHS, 2020), (Selbie, 2019). Attempts have been made in MS, to apply so-called 'precision' medicine, which involves using biological markers including radiology, MS sub-type, clinic status and other variables to determine ongoing management, but is dependent on availability and current technology. Used as part of earlier disease recognition, patients could be treated earlier in their disease course and preventative strategies could be implemented

without delay (Hansen and Okuda, 2018).

The film had a high level of self-perceived understanding and engagement, achieving its research aims, but there was less self-perceived understanding in a subcohort of those degree-educated who were also more likely to comment negatively.

The negative response was not seen on the same level in the MS Outpatients cohort compared to the MS Register cohort. A possible reason for the negative response in the MS Register cohort could partly be explained by the way it was delivered and received i.e. over the internet and the user's anonymity. There was also no opportunity for the MS Register participants to question the research before undertaking it. Directly approaching participants as part of the MS Outpatients cohort was a method for overcoming this and to clarify any questions that pwMS had. This in-person approach was more aligned to how the research was originally to be delivered as part of the RCT/routine care and could be adapted further for future application.

As described, an original research aim (chapter 4), was to initiate an RCT in order to fully test the film in routine care, but this did not happen. The primary reason was the feedback from the MS Register cohort. There were concerns that it would upset those newly diagnosed and therefore the decision was made – with the lead supervisor - not to proceed. Additional concerns were practical: the time and resources needed for achieving the numbers were substantial. The RCT could only work with the support of fellow staff; the number of participants to achieve was ambitious and there are a

limited number of people who are newly diagnosed to approach in the timeframe of a PhD. Finally, a research aim was to determine if the film influenced treatment initiation by way of follow-up a month later. This timepoint was based upon the mean of 29 days taken from the MS-DOUBT results where a treatment decision was initiated. However, it would be difficult to determine if the film itself had influenced a person to make a treatment decision and to what degree, as treatment decision-making is multi-factorial.

The compromise was to incorporate a smaller subcohort of pwMS from outpatient clinics from the local NHS Trust and for the research to be introduced in-person by the thesis author. Owing to the importance of the face-to-face consultation referenced in chapter 3, it was proposed that the human interaction may help explain the context of the research as well as give the research a "face". This approach is supported by a preference for face-to-face therapies over internet interventions (Apolinário-Hagen et al., 2018). Although the difference was not significant, the proportion of participants who left negative commentary was less in the MS Outpatients cohort versus the MS Register cohort with the largest proportion of neutral commentary across cohorts.

Whilst the film achieved its research aims, there are limitations that need acknowledging.

The YouTube analytics are an imperfect way of measuring user engagement and provide only an estimate of views. Indeed, the 'unique' users provided did not align

with the high level of user engagement in terms of commentary and the questions pertaining to self-perceived understanding of the concepts. It was not possible to relate individual users to level of engagement in terms of the amount of film footage viewed, only an average of the film watched could be obtained.

If the film was to be adapted again as part of a broader website, as was intended with the original website prototype, online tracking technology could be employed to determine what people watch of the film (if not in its entirety), whether they watch aspects of the film again and where they go on the website to obtain further information.

In addition, it was challenging to recruit the General Population and the overall figure was below the intended number – fortunately overall participant figures exceeded the research aims but how to better engage a general audience is a consideration for future research.

The film also needs context and user feedback pointed to the importance of the website content that supports it. With the further support of HCPs and the context of providing treatment options, it could be adapted for clinical application as part of an RCT, which remains the gold standard for evaluating DAs (Gillies et al., 2012).

It might never be possible to have a gold-standard intervention in MS that is universally understood, but through identifying how each intervention works and appeals to audiences (including audiences within an MS population and those

without the disease who are still significant in the decision-making process), there can be strides to target interventions to individuals or as part of a series of interventions that are staged depending on the person's requirements.

The film was purposefully recorded using green-screen technique so that the film could be modified further to respond to future evaluation. One application of this is that the narrative could remain, but the house and environment could be changed to appeal to other audiences. This would be in response to a selection of user feedback that queried the target demographic indicated by the perceived wealth of the home for example, or the environment could be adapted further to appeal to people in a different part of the world. The first edit of the house and environment was considered "too American" in look to appeal to a European audience for example.

In addition, the concepts could be related to aspects of other conditions that share the same multi-treatment considerations with healthcare repurcussions for treatment delay. Examples include diabetes and HIV. A similar study could be run to see if the results are consistent with those in MS.

Some user feedback pointed to a follow-up film that could be introduced to show explicitly the results of taking action as part of a series. One application of this could be to retell the story but with the intervention (perhaps in the form of a car MOT representing a clinical intervention and petrol indicating treatment).

In summary, determining robust research aims for a film delivered online has been challenging. Evaluation of a film that did not fit criteria for a DA or complex

intervention highlighted further that DAs need further definition as part of a still relatively young research field. Recruiting viewers from the General Population was also challenging, perhaps owing to the lack of personal investment in the disease.

5.3 Conclusion

The research presented in this thesis has incorporated two ethically approved studies and the opinion of >1200 pwMS.

The original research questions highlighted firstly, to better understand the role of decision-making for MS patients considering treatment options and this was achieved with the discovery of the associations described. Furthermore, the research has helped progress how DC is interpreted and its role in MS decision-making as a valid outcome measure – as was confirmed by a cross-sectional study and a prospective study in MS-DOUBT with follow-up of DC a year later.

DC has been progressed here by supplementing the existing, binary SURE measure with the SURE sub-measure and with the unvalidated DCG (created by the thesis author), which offered additional insight into the 'degree' of DC a person feels that they have by placing their perceived level of conflict between 0-100 on to an analogue scale.

In addition, as described, DC was measured across time here although it must be acknowledged that as decision making is a process, the question that DC is measuring could reasonably alter over time and this is an important consideration if it is to be

used as an outcome measure in the same population longitudinally. Here DC has been referenced as an outcome measure to treatment decision-making, but there is a lot of complexity interpreting the 'success' of a treatment. For example, a person may develop symptoms and side effects that influence their view of a treatment, the treatment choice can be taken away from the patient when a treatment is stopped on grounds of safety and then there is no personal comparator for an individual to know if the decision they have made is the right one, aside from efficacy and perceived improvement and sustainability of quality of life. Indeed, how a decision is best measured and whether it can be deemed 'successful' is perceived differently in individuals and makes it challenging to produce a consensus approach.

DC affected half of the cohort studied. An advantage of administering the SURE scale is that it is a shortened version of the DCS and therefore it is quick to administer. It could be used in clinical practice prior to consultations to gauge where conflict lies by using the sub-scale of questions to pinpoint where most clarity or attention is needed. The consultation could then be focused on resolving this area of conflict and DC could again be measured post-consultation and at subsequent clinic visits to determine if DC has resolved in the individual.

Additional research aims were to investigate the relationship of image and narrative and how it is presented and its effects on decision-making; furthermore, to identify different streams of information and how presentation is absorbed and interpreted by individuals. These research aims were explored through film analogy and it was discovered that people at different levels of education and disease course both had

high levels of understanding but different interpretations of the information conveyed.

The research was less successful in determining if treatment decision-making could be directly influenced by way of the film intervention, as an RCT was not carried out in order to measure its efficacy versus a control group. The film and how such interventions are best interpreted is an area of focus for future research as so-called 'complex' interventions come under many guises.

The negative response to the film suggested it needed further evaluation to determine if it was ethically viable to proceed, hence a smaller cohort of MS patients were approached in the outpatient setting to gain insight into how the film might be received differently if the film was discussed in-person as opposed to the MS Register cohort whose evaluation was entirely anonymous and online.

The results of the MS outpatient arm, although numbers were relatively small, were promising in that proportionately the negative response was not as great versus the MS Register and the way the film research was delivered in-person with the opportunity to cover the additional context required, could potentially have contributed to this.

Furthermore it became apparent that executing the RCT in the timeframe of a PhD was too ambitious. The reasons were twofold: the paucity of newly diagnosed individuals would likely have meant a multi-centre design would be required and the resources were not there to achieve this at this time.

With further evaluation, funding and the support of MS colleagues, the film could be tested in an outpatient setting as part of an RCT design. The film could be evaluated versus routine care and the intervention arm of participants could be followed up at a later time point to determine their level of understanding to the film's concepts and any subsequent research that they may have carried out could be recorded. The film's impact in terms of influence on treatment decision-making could then be further evaluated.

Internet-based interventions are challenging to evaluate in part due to the organic and unregulated nature of the Internet, making it difficult to control the environment being assessed. However, the research here still identified the importance that the consultation plays, and the role of SDM within it in resolving DC and commencing treatment. Therefore, further research into SDM and other components allowing for insight into the clinical encounter appears to be a valuable investment.

As the treatment spectrum grows in MS, systems must be in place to respond to the evolving needs of pwMS at different stages of the disease (especially as treatments aimed at a progressive audience are likely to become more common). The MS Register population also highlighted a number of unmet needs. HCPs will be required to meet the demands of a changing prescribing environment married to time pressures of an already pressured healthcare system, as well as fulfilling macro-led expectations, dictating how information should best be communicated in the form of SDM with the patient at the centre of care.

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Appendices

Appendix A - A matrix of RCTs testing DAs in MS (Wilkie, 2019).

Study Overview	Intervention versus Control	Target Group	Outcome measures	Measurements, Results & Follow-up	Refs
A multi-centre German-led RCT evaluating a training module called 'doktormitSDM' to improve implantation of SDM as measured from three perspectives (physician/patient/observer)	A manual explaining SDM highlighting 15 skills, a video connected to the manual showing how the skills are implemented in practice, face-to-face feedback. VS Control group without the training as part of routine care. The study was designed so that the control group would receive the same training at a later time-point.	152 consultations covering seven medical specialties	SDMmass (based on MAPPIN'SDM) to determine agreement between parties described.	SDMmass showed significant increase in the IG group versus the control group.	(Geiger et al., 2017)
A multi-centre German-led RCT investigating the effects of a structured educational programme on relapse management in MS (duration two years). Aim was to evaluate the Evidence-Based Self-management In MS (EBSIMS).	A 30-page brochure, evaluating relapse management. Participants took part in a four to five hour nurse-led training session with the option of prescribing steroids to treat the relapse. VS Control group participants were given a leaflet about relapse treatment, with the option of oral steroids to treat the relapse.	150 Patients with RRMS, with at least two relapses in the last 24 months or at least one relapse in the last 12 months.	Primary aim was relapse percentage without steroids or with oral steroids within two years of follow-up. Secondary aims included: time to initiate treatment and features of taking steroid treatments, costs, recording of patient autonomy preferences and changes, QoL, relapse severity AEs, etc.	Perceived patient autonomy and knowledge of risk was reported as higher in the intervention group. On the strength of the RCT, the 'train-the trainer' programme has since been followed up in clinical practice instructing 31 HCPs and 261 people with MS (Köpke and Heeson, 2011).	(Kopke et al., 2009);

Germany study: Informed Shared Decision making In Multiple Sclerosis immunotherapy (ISDIMS). Aim was to develop an evidence- based DA on MS immunotherapy with an RCT looking at the effects of an evidence-based DA on decision-making about immunotherapies in MS over a year.	A 120-page booklet containing treatment options and an interactive worksheet pre-consultation. People with different types of MS were directed to the relevant section of the DA. VS. The control group received standard information recommended by the 'German Self-Help Organisation' incorporating self-help leaflets.	297 MS patients were recruited Oct 2004-Feb 2006 considering a new immunotherapy and randomly assigned to one of two treatment groups are willing to reconsider a decision (no selection of certain disease courses). Patients were recruited via advertisements in local newspapers	Primary end-point was whether role preferences' were realised defined as the difference between autonomy preferences pre-intervention & post appointment. Secondary endpoints included treatment choice. SDM was also measured as part of decision evaluation in addition to other information sources, time to treatment initiation, level of disease activity, disability status, etc.	CPS was used as a measurement tool to evaluate if patient's role preference pre-physician-patient encounter versus post was realised. Results showed that no difference was shown between groups re: role preference (IG 49%, CG 51%, P= 0.71).	(Kasper et al., 2008);
Effectiveness of an interview in pwMS newly-diagnosed called 'SIMS'. The rationale was based on knowledge deficit around the diagnosis stage. An Italian RCT assessing patient knowledge and their satisfaction with the information provided, via an information aid, given within 15 days of communicating an MS diagnosis	The add-on interview was conducted by trained neurologists (approximately one hour in length), during which information about MS was discussed with the support of a bespoke CD. The information was tailored to the individual needs of the patient who were also given a booklet containing the information discussed and provided. VS Routine care	120 pwMS newly diagnosed from five Italian centres	MS Knowledge and Satisfaction with care at one and six months post-intervention.	At month 1, 50% (30/60 intervention subjects) achieved primary endpoint compared to 8/60 controls equivalent to 95% CI and P<0.001).	(Borreani et al., 2011); (Giordano A, 2014)

(defined as six months).					
German-based patient education programme for early MS called 'PEPADIP' evaluated with a multi-centre RCT assessing the effects of an evidence-based patient education programme on MS diagnosis, prognosis and early treatment aimed at pwMS a year from diagnosis.	Intervention was a 60-page educational booklet on MS diagnosis, prognosis and early treatment and a four-hour teaching programme VS Control: stress management training and leaflet covering diagnosis, prognosis and early treatment.	192 early MS/newly diagnosed patients	Primary aim was defined as informed choice about initiation or continuation of treatment at six months; Follow-up comprised of an adapted form of the Multidimensional Measure of Informed Choice. Secondary aims included control beliefs using KKG questionnaire, CPS, DCS, depression/anxiety, QoL, recording disease progression, newly initiated and those who discontinued treatments (participants on treatment 12 months post-intervention), assessed by telephone interview at randomisation then every three months up to one year, resource costs	Follow-up includes a study (PEPIMS) evaluating the programme with patients in rehab clinics (Heesen et al., 2011).	(Köpke et al., 2014).

Appendix B – Questionnaire for 'MS Conference Attendees' cohort (2014) and adaptions for 'on treatment' cohort (2015)

Section 1

Q1. What is your gender?	1. Male ☐	2. Female ☐
Q2. What is your age?	1. 18 to 24 ☐ 2. 25 to 34 ☐ 3. 35 to 44 ☐ 4. 45 to 54 ☐	

	5. 55 to 64 ☐ 6. 65 to 75 ☐ 7. 75 or older ☐	
Q3. What is your ethnicity?	1. White - British ☐ 2. White - Irish ☐ 3. Any other white background ☐ 4. Mixed – White & Black Caribbean ☐ 5. Mixed – White & Black African ☐ 6. Mixed – White & Asian ☐ 7. Any other mixed background ☐ 8. Asian or Asian British - Indian ☐	9. Asian or Asian British - Pakistani ☐ 10. Asian or Asian British - Bangladeshi ☐ 11. Any Other Asian Background ☐ 12. Black or Black British - Caribbean ☐ 13. Black or Black British - African ☐ 14. Any Other Black background ☐ 15. Chinese ☐ 16. Any other ethnic group (please specify) ☐ _____
Q4. Marital Status	1. Single ☐ 2. Married ☐ 3. Divorced ☐ 4. Separated ☐	5. Co-habiting ☐ 6. Civil partnership☐ 7. Same-sex marriage ☐ 8. Widowed ☐
Q5. How did you access this survey?	1. Smart Phone ☐ 2. PC ☐ 3. Laptop ☐ 4. Other (please specify) ☐_____	
Q6. From where are you accessing this survey?	1. Home ☐ 2. Work ☐ 3. On the move ☐ 4. Other (please specify ☐ _____	
Q7 Which of the following best describes your employment status?	1. Employed ☐ 2. Home maker ☐ 3. Retired ☐ 4. Student ☐	

	5. Unemployed ☐ 6. Other circumstances (please state) _____		
Q8. Type of MS	1. Relapsing-Remitting ☐ 2. Secondary Progressive ☐ 3. Primary Progressive ☐ 4. Clinically Isolated Syndrome (MS not diagnosed) ☐ 5. Not known ☐		
Q9. Year of MS Diagnosis (if known)	1. Please state_____ 2. Don't know ☐		
Q10. Under which NHS Trust is your neurology care registered?	1. Imperial College Healthcare NHS Trust (incorporating Charing Cross, Hammersmith, Western Eye & St Mary's Hospitals) ☐	2. Other London (eg. Kings, Queens' Square, etc) ☐ Please specify _____	3. Other UK Trust ☐ Please specify _____

Section 2:

Q11. The following table lists MS treatments currently available either licensed or in development (eg. as part of a clinical trial). For each treatment, please tick one answer.

1. Natalizumab (Tysabri)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
2. Fingolimod (Gilenya)	1. Currently receiving	2. Have tried this treatment in the past but	3. I have knowledge of this treatment but have never been	4. I have no knowledge of this treatment and have never been	5. I am either on this treatment or placebo as part of a

	this treatment ☐	now stopped ☐	prescribed it ☐	prescribed it ☐	clinical trial ☐
3 Alemtuzumab (Lemtrada)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
4. Beta interferon (eg. Avonex, Rebif, Betaferon, Extavia)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
5. Dimethyl Fumerate (Tecfidera/BG-12)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
6. Glatiramer Acetate (Copaxone)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
7. Teriflunomide (Aubagio)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
8. Laquinimod	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐

9. Stem Cells	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
10. Azathioprine	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
11. IVIg (intravenous innumoglobulin)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
12. Mitoxantrone	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
13. Cyclophosphamide	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
14. Zenapax (Daclizumab)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
15. Ocrelizumab	1. Currently receiving	2. Have tried this treatment in the past but	3. I have knowledge of this treatment but have	4. I have no knowledge of this treatment and have	5. I am either on this treatment or placebo as

	this treatment ☐	now stopped ☐	never been prescribed it ☐	never been prescribed it ☐	part of a clinical trial ☐

Q12. With reference to treatment, which of the following options best reflects your *current* situation?

Please tick one box.

1. Satisfied to continue with existing treatment ☐	2. On treatment but considering a treatment switch ☐	3. Not on treatment but considering treatment options ☐	4. Not on treatment and not considering treatment ☐

Q.13 Further to the answer you gave (above) for Q12 referencing treatment choice:

1. Do you feel sure about the best choice for you?	1. Yes ☐	2. No ☐
2. Do you know the benefits and risks of each option?	1. Yes ☐	2. No ☐
3. Are you clear about which benefits and risks matter most to you?	1. Yes ☐	2. No ☐
4. Do you have enough support and advice to make a choice?	1. Yes ☐	2. No ☐

Section 3

Q14. Which of the following factors are influential in selecting treatment?

1. Route of administration eg. Injectable, infusion, oral	1. Highly influential ☐	2. Partly influential ☐	3. Not at all influential ☐	4. Unsure/Don't Know ☐
2. Frequency of administration eg. Daily, weekly,	1. Highly influential ☐	2. Partly influential ☐	3. Not at all influential ☐	4. Unsure/Don't Know ☐

monthly commitment				
3. Side Effects from taking treatment eg. rash, fatigue, etc	1. Highly influential ☐	2. Partly influential ☐	3. Not at all influential ☐	4. Unsure/Don't Know ☐
4. Risk factors from staying on treatment eg. PML risk, macular edema risk, etc.	1. Highly influential ☐	2. Partly influential ☐	3. Not at all influential ☐	4. Unsure/Don't Know ☐
5 Pregnancy or desire to start a family	1. Highly influential ☐	2. Partly influential ☐	3. Not at all influential ☐	4. Unsure/Don't Know ☐
6 Other reasons not listed	Please specify			

Section 4

Q15. Based upon your current treatment status (even if you are not on treatment), please show how you feel about these statements by selecting a single options from each row of statements below:

1. It was the right decision	1 Strongly Agree ☐	2 Agree ☐	3 Neither Agree Nor Disagree ☐	4 Disagree ☐	5 Strongly Disagree ☐
2. I regret the choice that was made	1 Strongly Agree ☐	2 Agree ☐	3 Neither Agree Nor Disagree ☐	4 Disagree ☐	5 Strongly Disagree ☐
3. I would go for the same choice if I had to do it over again	1 Strongly Agree ☐	2 Agree ☐	3 Neither Agree Nor Disagree ☐	4 Disagree ☐	5 Strongly Disagree ☐
4. The choice did me a lot of harm	1 Strongly Agree ☐	2 Agree ☐	3 Neither Agree Nor Disagree ☐	4 Disagree ☐	5 Strongly Disagree ☐

5. The decision was a wise one	1 Strongly Agree ☐	2 Agree ☐	3 Neither Agree Nor Disagree ☐	4 Disagree ☐	5 Strongly Disagree ☐

Section 5

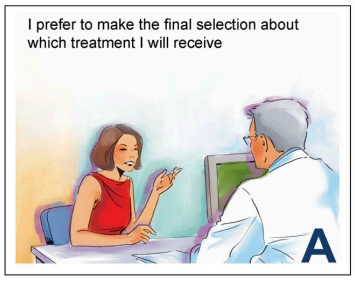
Q16. Please rate how *influential* you think the following people are with reference to making a decision about *starting or stopping treatment*

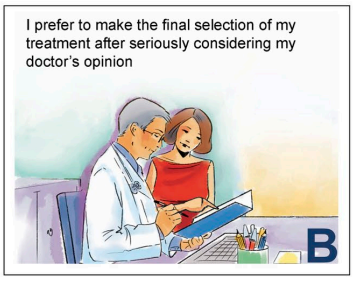
1. GP	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
2. Consultant neurologist	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
3. Partner	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
4. Other close relatives	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
5. Friends	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
6. Employer	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
7. Faith or Religious leader eg. Rabbi, priest, Please specify _____	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
8 Other	Please state (if applicable)			

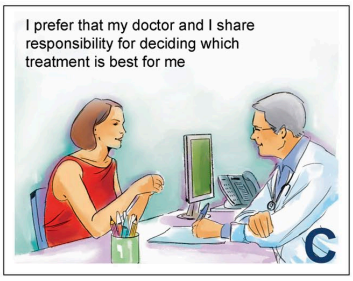
Section 6

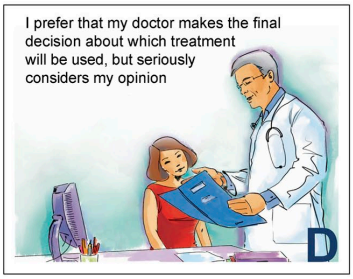
Q17. Which of the following scenarios best fits how you would usually reach a decision about treatment either now or in the past?

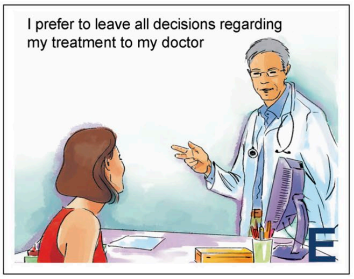
A - ☐ B - ☐ C - ☐ D - ☐ E - ☐











Additional questions were added to the 'on treatment' cohort questionnaire as follows:

Section 3 – as before with additional option 6 re: effectiveness of treatment:

Q14. Which of the following factors are influential in selecting treatment?

Effectiveness of treatment	1. Highly influential ☐	2. Partly influential ☐	3. Not at all influential ☐	4. Unsure/Don't Know ☐
Other reasons not listed	Please specify below			

Section 6: wording was changed to:

Q17. Which of the following scenarios (see pictures that follow) best fits how you would usually reach a decision about treatment either now or in the past? Please order your preference 1-5 where 1 represents most preferable and 5 represents the least preferred option.

A - ☐ B - ☐ C - ☐ D - ☐ E - ☐

Section 7 was added:

Q18. Thinking about your most recent consultation at Charing Cross Hospital with the consultant neurologist (referenced in the cover letter), how good was the doctor at each of the following? Please select one choice for each row.

Giving you enough time	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐
Asking about your symptoms	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐
Listening to you	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐
Explaining tests and treatments	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐
Involving you in decisions about your care	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐
Treating you with care and concern	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐
Taking your problems seriously	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐

Q19. Please state the name of the consultant that reviewed you (if different from the cover letter)

Q20. Did you have confidence and trust in the doctor that you saw?

1. Yes, definitely ☐

2. Yes, to some extent ☐

3. No, not at all ☐

4. Don't know, can't say ☐

This marks the end of the questionnaire. Please kindly double-check that you have answered every question as described.

Once again, thank you for taking the time to complete the research.

References

Légaré F, Kearing S, Clay K, Gagnon S, D'Amours D, Rousseau M, O'Connor AM. Are you SURE? Assessing patient decisional conflict with a 4-item screening test. Can Fam Physician 2010; 56:e308-314.

O'Connor AM. User Manual – Decision Regret Scale [document on the Internet]. Ottawa: Ottawa Hospital Research Institute; © 1996 [modified 2003; cited 2014]. 3 p. Available from http://decisionaid.ohri.ca/docs/develop/User_Manuals/UM_Regret_Scale.pdf

Solari A, Giordano A, Kasper J, Drulovic J, van Nunen A, et al. (2013) Role Preferences of People with Multiple Sclerosis: Image-Revised, Computerized Self-Administered Version of the Control Preference Scale. PLoS ONE 8(6): e66127. doi:10.1371/journal.pone.0066127

Appendix C – Questionnaires used for 'offered treatment' cohort (MS-DOUBT study)

OFFICE USE ONLY			
STUDY ID PARTICIPANT		STUDY PARTICIPANT IDENTIFIER	

Q.1 With reference to treatment, which of the following options best reflects your *current* situation? Please tick one box only.

1. Satisfied to continue with existing treatment ☐	2. On treatment but considering a treatment switch ☐	3. Not on treatment but considering treatment options ☐	4. Not on treatment and not considering treatment ☐

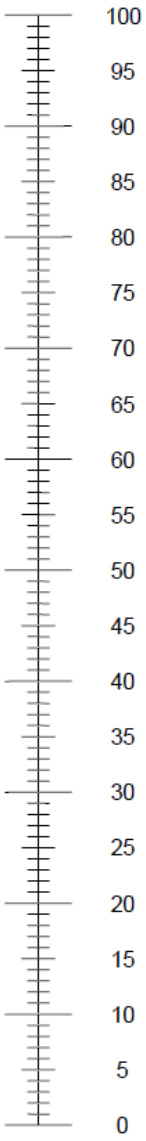
Q.2 Further to the answer you gave (above) referencing treatment choice:

1. Do you feel sure about the best choice for you?	1. Yes ☐	2. No ☐
2. Do you know the benefits and risks of each option?	1. Yes ☐	2. No ☐
3. Are you clear about which benefits and risks matter most to you?	1. Yes ☐	2. No ☐
4. Do you have enough support and advice to make a choice?	1. Yes ☐	2. No ☐

Q.3. We would like to find out what your level of decisional conflict is <u>today referencing a treatment decision that you need to make now or in the future</u>

Please indicate with **X** on the scale (right) where you think your level of decision conflict falls where 0 represents no decisional conflict and 100=the highest decisional conflict you can imagine.

Please then write the number you marked on the scale into the box below.



If you have consented to be involved in the research, please fill out the following information to enable us to contact you in the future. Thank you.

CONTACT SHEET

FIRST NAME	
SURNAME	
DATE OF BIRTH	
NHS NUMBER (IF KNOWN)	
HOME ADDRESS (inc. postcode)	
HOME TELEPHONE NUMBER	
MOBILE NUMBER	
E-MAIL ADDRESS	
PREFERENCE DAY(S) AND	

TIME(S) TO BE CONTACTED	

OFFICE USE ONLY			
STUDY ID		**STUDY PARTICIPANT IDENTIFIER**	

Section 1 (Clinical Encounter)

Q1. Thinking about your most recent consultation at Charing Cross Hospital with the consultant neurologist, how good was the doctor at each of the following? Please select one choice for <u>each</u> row.

Giving you enough time	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐
Asking about your symptoms	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐
Listening to you	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐
Explaining tests and treatments	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐

Involving you in decisions about your care	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐
Treating you with care and concern	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐
Taking your problems seriously	1 Very good ☐	2 Good ☐	3 Neither good nor poor ☐	4 poor ☐	5 Very poor ☐	Doesn't apply ☐

Q.2. Please state the name of the consultant that reviewed you _____

Q.3. Did you have confidence and trust in the doctor that you saw?

1. Yes, definitely ☐
2. Yes, to some extent ☐
3. No, not at all ☐
4. Don't know, can't say ☐

(Croker et al., 2013)], (Roberts et al., 2014)

Section 2

This questionnaire assesses your knowledge of multiple sclerosis. Please read each statement and tick the letter that corresponds to the answer you consider correct. Please answer all statements, and tick only one answer for each statement.

1 Multiple sclerosis is a disease of:

a) The central nervous system
b) All body organs
c) Don't know

2 The central nervous system consists of:

a) Brain
b) Brain and spinal cord
c) Brain, spinal cord and optic nerves
d) Brain and peripheral nerves
e) Don't know

3 In the UK, multiple sclerosis affects:

a) About 100 people (one in 500,000)
b) About 1000 people (one in 50,000)
c) About 50,000 people (one in 1000)
d) Don't know

4 Multiple sclerosis significantly shortens lifespan:

a) True
b) False
c) Don't know

5 Multiple sclerosis is a disease of the immune system:

a) True
b) False
c) Don't know

6 Multiple sclerosis is a contagious disease:

a) True
b) False
c) Don't know

7 The causes of multiple sclerosis are still not completely clear. The most important causes seem to be:

a) Diet and smoking
b) Alcohol consumption and infection
c) Infection and genetic factors
d) Don't know

8 A parent with multiple sclerosis passes the disease on to his/her children via the chromosomes:

a) True
b) False
c) Don't know

9 The likelihood of a relative of a patient with multiple sclerosis having the disease is:

a) The same as a person with no MS in the family
b) Slightly higher (less than 5%) than a person with no MS in the family
c) Much higher (greater than 30%) than a person with no MS in the family
d) Don't know

10 Multiple sclerosis injures:

a) The myelin
b) The axon (nerve fibre)
c) Both myelin and axon
d) Don't know

11 Multiple sclerosis can manifest at any age, but typically occurs:

a) Before 20 years
b) Between 20–40 years
c) Between 40–60 years
d) Don't know

12 Multiple sclerosis occurs in the UK:

a) Women and men about equally
b) Men about twice as often as women
c) Women about twice as often as men
d) Don't know

13 Like the insulation of an electric wire, myelin facilitates and speeds up the transmission of nervous impulses:

a) True
b) False
c) Don't know

14 At present there is no single test/examination that can diagnose multiple sclerosis with certainty:

a) True
b) False
c) Don’t know

15 Magnetic resonance imaging (MRI) is the examination most commonly used to confirm the multiple sclerosis diagnosis:

a) True
b) False
c) Don’t know

16 Intra-venous injection of contrast (gadolinium) during MRI reveals lesions that are:

a) Old
b) Recent
c) Both old and recent
d) Don’t know

17 MRI is repeated at intervals to better follow disease course over time:

a) True
b) False
c) Don’t know

18 Lumbar puncture is performed to assess the cerebrospinal fluid for antibodies (oligoclonal bands) that indicate an immune reaction typical of multiple sclerosis:

a) True
b) False
c) Don’t know

19 Lumbar puncture is repeated at intervals to better follow disease course over time:

a) True
b) False
c) Don’t know

20 A definite diagnosis of multiple sclerosis:

a) Can require repetition of MRI
b) Is always possible at first disease attack
c) Don’t know

21 ‘‘Relapsing–remitting’’ multiple sclerosis is characterized by:

a) Slow and progressive deterioration in functioning (increase in disability) followed, after months or years, by attacks (relapses)

b) Repeated attacks (relapses) at more or less frequent intervals
c) Don't know

22 ''Benign'' multiple sclerosis is characterized by:

a) Minimal deterioration in functioning (disability) one year after disease onset
b) Minimal deterioration in functioning (disability) 15–20 years after disease onset
c) Don't know

23 Pregnancy worsens multiple sclerosis:

a) True
b) False
c) Don't know

24 At present there is no treatment that can cure multiple sclerosis:

a) True
b) False
c) Don't know

25 Disease modifying drugs are effective in:

a) ''Relapsing–remitting'' multiple sclerosis
b) ''Primary progressive'' multiple sclerosis
c) Both ''relapsing–remitting'' and ''primary progressive'' multiple sclerosis
d) Don't know

Section 3

The following table lists MS treatments currently available either licensed or in development (eg. as part of a clinical trial). <u>For each treatment, please tick one answer per row that best reflects your current status and knowledge.</u>

1. Natalizumab (Tysabri)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
2. Fingolimod (Gilenya)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never	4. I have no knowledge of this treatment and have never been	5. I am either on this treatment or placebo as part of a

			been prescribed it ☐	prescribed it ☐	clinical trial ☐
3 Alemtuzumab (Lemtrada)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
4. Beta interferon (eg. Avonex, Rebif, Betaferon, Extavia)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
5. Dimethyl Fumerate (Tecfidera/BG-12)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
6. Glatiramer Acetate (Copaxone)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
7. Teriflunomide (Aubagio)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
8. Laquinimod	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐

9. Stem Cells	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
10. Azathioprine	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
11. IVIg (intravenous innumoglobulin)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
12. Mitoxantrone	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
13. Cyclophospham ide	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐
14. Zenapax (Daclizumab)	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐

15. Ocrelizumab	1. Currently receiving this treatment ☐	2. Have tried this treatment in the past but now stopped ☐	3. I have knowledge of this treatment but have never been prescribed it ☐	4. I have no knowledge of this treatment and have never been prescribed it ☐	5. I am either on this treatment or placebo as part of a clinical trial ☐

<u>The 9-item Shared Decision Making Questionnaire (SDM-Q-9)</u>
Please indicate which health complaint/problem/illness the consultation was about e.g. Multiple Sclerosis (MS)

Please indicate which decision was made: eg. to start treatment, end treatment, continue treatment, no decision was made concerning treatment

Nine statements related to the decision-making in your consultation are listed below. For each statement please indicate how much you agree or disagree.

1. My doctor made clear that a decision needs to be made.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
2. My doctor wanted to know exactly how I want to be involved in making the decision.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
3. My doctor told me that there are different options for treating my medical condition.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
4. My doctor precisely explained the advantages and disadvantages of the treatment options.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**

5. My doctor helped me understand all the information.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
6. My doctor asked me which treatment option I prefer.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
7. My doctor and I thoroughly weighed the different treatment options.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
8. My doctor and I selected a treatment option together.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
9. My doctor and I reached an agreement on how to proceed.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**

February 2012

Reference:

Kriston, L., Scholl, I., Hölzel, L., Simon, D., Loh, A. & Härter, M. (2010). The 9-item Shared Decision Making Questionnaire (SDM-Q-9). Development and psychometric properties in a primary care sample. Patient Education and Counseling, 80 (1), 94-99.

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The 9-item Shared Decision Making Questionnaire (SDM-Q-Doc)

Please indicate which health complaint/problem/illness the consultation was about e.g. Multiple Sclerosis (MS)

Please indicate which decision was made: eg. to start treatment, end treatment, continue treatment, no decision was made concerning treatment

Please record EDSS Score

Nine statements related to the decision-making in your consultation are listed below. For each statement please indicate how much you agree or disagree.

1. I made clear to my patient that a decision needs to be made.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
2. I wanted to know exactly from my patient how he/she wants to be involved in making the decision.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
3. I told my patient that there are different options for treating his/her medical condition.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**

4. I precisely explained the advantages and disadvantages of the treatment options to my patient.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
5. I helped my patient understand all the information.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
6. I asked my patient which treatment option he/she prefers.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
7. My patient and I thoroughly weighed the different treatment options.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
8. My patient and I selected a treatment option together.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**
9. My patient and I reached an agreement on how to proceed.					
Completely disagree ☐	**Strongly disagree ☐**	**Somewhat disagree ☐**	**Somewhat agree ☐**	**Strongly agree ☐**	**Completely agree ☐**

February 2012

Reference: Kriston, L., Scholl, I., Hölzel, L., Simon, D., Loh, A. & Härter, M. (2010). The 9-item Shared Decision Making Questionnaire (SDM-Q-9). Development and psychometric properties in a primary care sample. Patient Education and Counseling, 80 (1), 94-99.

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Please note in this section that you are occasionally asked to write in your answer.

If you do not feel comfortable about answering any question in this section, please do not provide an answer.

Section 1

Q1. What is your gender?	1. Male ☐	2. Female ☐
Q2. What is your year of birth?		
Q3. How would you describe yourself ethnically?	1. White – UK heritage ☐ 2. White - Other ☐ 3. Pakistani ☐ 4. Bangladeshi ☐ 5. Indian ☐ 6. Black – African heritage ☐ 7. Black – Caribbean heritage ☐ 8. Chinese ☐	9. Other ☐
Q4. What sort of family religious background do you have?	1. Christian - Protestant ☐ 2. Christian – Roman Catholic ☐ 3. Christian - Other ☐ 4. Muslim ☐ 5. Hindu ☐ 6. Jewish ☐ 7. Buddhist ☐ 8. Other belief system ☐	9. None at all ☐
Q5. And with which religion would you say you most closely identify now?	1. Christian - Protestant ☐ 2. Christian – Roman Catholic ☐ 3. Christian - Other ☐ 4. Muslim ☐ 5. Hindu ☐ 6. Jewish ☐ 7. Buddhist ☐	9. None at all ☐

	8. Other belief system ☐
Q6. How many children do you have?	1. None ☐ 2. 1 ☐ 3. 2 ☐ 4. 3 ☐ 5. 4 ☐ 6. 5 ☐ 7. 5+ ☐
Q7. Your Marital Status?	1. Single ☐ 2. Married ☐ 3. Divorced/Separated ☐ 4. Widowed ☐ 5. Civil partnership☐ 6. Other ☐
Q8. Your current occupation?	1. Private sector, manufacturer ☐ 2. Private sector, service company ☐ 3. Armed forces ☐ 4. Health service ☐ 5. Other public sector ☐ 6. Voluntary sector/charities ☐ 7. Academic/teaching ☐ 8. Self-employed ☐ 9. Not employed ☐ 10. Other ☐
Q9. How religious are you? On a scale of 1-7, where 1=Not Religious At All 4=Average 7=Very Religious	Please write in your score here or Doesn't Apply:
Q10. What are your political convictions? On a scale of 1-7, where 1=Strongly Left Wing 4=Neither 7=Strongly Right Wing	Please write in your score here or Doesn't Apply:
Q11. How happy in your job are you? On a scale of 1-7, where 1=Not At All Happy 4=Average 7=Very Happy	Please write in your score here or Doesn't Apply:
Q12. Your highest educational qualification?	1. Secondary education: GCSE/O-Level or similar ☐ 2. Higher education: A-Level or similar ☐ 3. Undergraduate Degree (eg. BA, BSc, etc) ☐ 5. Post-graduate Degree (eg. MA, MSc, MBA, etc) ☐

	6. Doctorate (PhD) ☐ 7. Other ☐
Q13. Type of MS	1. Relapsing-Remitting ☐ 2. Secondary Progressive ☐ 3. Clinically Isolated Syndrome (MS not diagnosed) ☐ 4. Not known ☐
Q14. Year of MS Diagnosis (if known)	1. Please state_____ 2. Don't know ☐

Section 2

Which of the following factors are influential in selecting treatment? Please tick one box per row.

1. Route of administration eg. Injectable, infusion, oral	1. Highly influential ☐	2. Partly influential ☐	3. Not at all influential ☐	4. Unsure/Don't Know ☐
2. Frequency of administration eg. Daily, weekly, monthly commitment	1. Highly influential ☐	2. Partly influential ☐	3. Not at all influential ☐	4. Unsure/Don't Know ☐
3. Side effects from taking treatment eg. rash, fatigue, etc	1. Highly influential ☐	2. Partly influential ☐	3. Not at all influential ☐	4. Unsure/Don't Know ☐
4. Risk factors from staying on treatment eg. PML risk (a rare viral disease of the brain), macular edema risk (affecting vision), etc.	1. Highly influential ☐	2. Partly influential ☐	3. Not at all influential ☐	4. Unsure/Don't Know ☐
5. Pregnancy or desire to start a family	1. Highly influential ☐	2. Partly influential ☐	3. Not at all influential ☐	4. Unsure/Don't Know ☐

6. Effectiveness of treatment	1. Highly influential ☐	2. Partly influential ☐	3. Not at all influential ☐	4. Unsure/Don't Know ☐
7. Other reasons not listed	Please specify (if applicable):			

Section 3

Based upon your current treatment status (even if you are not on treatment), please show how you feel about these statements by selecting a single option from each row of statements below:

1. It was the right decision	1 Strongly Agree ☐	2 Agree ☐	3 Neither Agree Nor Disagree ☐	4 Disagree ☐	5 Strongly Disagree ☐
2. I regret the choice that was made	1 Strongly Agree ☐	2 Agree ☐	3 Neither Agree Nor Disagree ☐	4 Disagree ☐	5 Strongly Disagree ☐
3. I would go for the same choice if I had to do it over again	1 Strongly Agree ☐	2 Agree ☐	3 Neither Agree Nor Disagree ☐	4 Disagree ☐	5 Strongly Disagree ☐
4. The choice did me a lot of harm	1 Strongly Agree ☐	2 Agree ☐	3 Neither Agree Nor Disagree ☐	4 Disagree ☐	5 Strongly Disagree ☐
5. The decision was a wise one	1 Strongly Agree ☐	2 Agree ☐	3 Neither Agree Nor Disagree ☐	4 Disagree ☐	5 Strongly Disagree ☐

Section 4 (IPS)

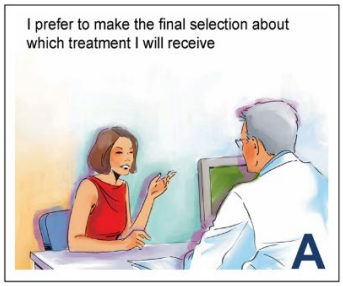
Please rate how *influential* you think the following people are with reference to making a decision about *starting or stopping treatment*

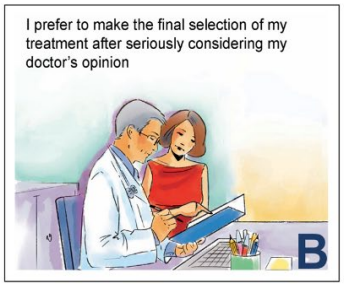
1. GP	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
2. Consultant neurologist	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
3. MS Specialist Nurse	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
4. Physiotherapist	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
5. Occupational Therapist	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
6. Partner	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
7. Other close relatives	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
8. Friends	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
9. Employer	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
10. Faith or Religious leader eg. Rabbi, priest, Please specify _____	1. Highly influential ☐	2. Fairly influential ☐	3. Applies to me but no influence ☐	4. Doesn't apply to me ☐
10. Other	Please specify (if applicable):			

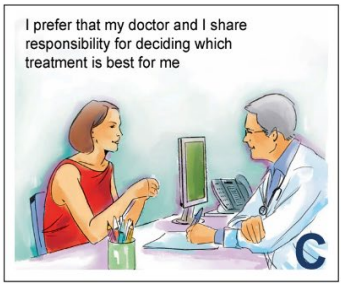
Section 5

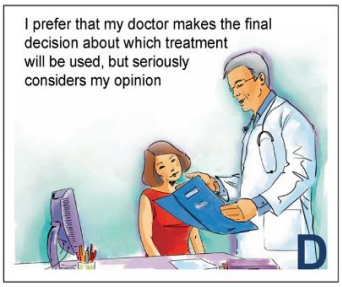
Which of the following scenarios best fits how you would usually reach a decision about treatment either now or in the past? Please pick one answer only

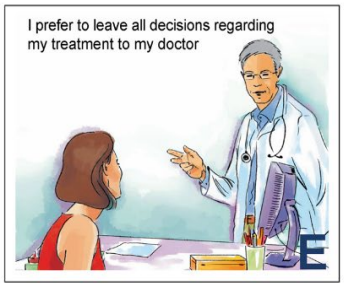
A - ☐ B - ☐ C - ☐ D - ☐ E - ☐











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Solari A, Giordano A, Kasper J, Drulovic J, van Nunen A, et al. (2013) Role Preferences of People with Multiple Sclerosis: Image-Revised, Computerized Self-Administered Version of the Control Preference Scale. PLoS ONE 8(6): e66127. doi:10.1371/journal.pone.0066127

Section 6 – HADS questionnaire was reviewed in this section of the questionnaire but has been removed at the request of the creator due to copyright issues.

Section 7

Below are some statements that people sometimes make when they talk about their health. Please

indicate how much you agree or disagree with each statement as it applies to you personally by circling your answer. There are no right or wrong answers, just what is true for you. If the statement does not apply to you, circle N/A.

I am the person who is responsible for taking care of my own health	Disagree strongly	Disagree	Agree	Agree strongly	N/A
Taking an active role in my own health care is the most important thing that affects my health	Disagree strongly	Disagree	Agree	Agree strongly	N/A
I am confident I can help prevent or reduce problems associated with my health	Disagree strongly	Disagree	Agree	Agree strongly	N/A
I know what each of my prescribed medications do	Disagree strongly	Disagree	Agree	Agree strongly	N/A
I am confident that I can tell whether I need to go to the doctor or whether I can take care of a health problem myself	Disagree strongly	Disagree	Agree	Agree strongly	N/A
I am confident that I can tell a doctor concerns I have even when he or she does not ask	Disagree strongly	Disagree	Agree	Agree strongly	N/A
I am confident that I can carry out medical treatments I may need to do at my home	Disagree strongly	Disagree	Agree	Agree strongly	N/A
I understand my health problems and what causes them	Disagree strongly	Disagree	Agree	Agree strongly	N/A
I know what treatments are available for my health problems	Disagree strongly	Disagree	Agree	Agree strongly	N/A
I have been able to maintain (keep up with) lifestyle changes, like healthy eating or exercising	Disagree strongly	Disagree	Agree	Agree strongly	N/A
I know how to prevent problems with my health	Disagree strongly	Disagree	Agree	Agree strongly	N/A
I am confident I can figure out solutions when new problems arise with my health	Disagree strongly	Disagree	Agree	Agree strongly	N/A
I am confident that I can maintain lifestyle changes, like healthy eating and exercising, even during times of stress	Disagree strongly	Disagree	Agree	Agree strongly	N/A

Section 8 – TEIQue was reviewed by patients at this point in the questionnaire, however permission has been denied by the creator to publish here the questionnaire in its entirety.

RIKNO

- Risk knowledge questionnaire in MS-

This questionnaire assesses your knowledge of MS. It was especially developed to assess risk knowledge in education programmes for patients who are considering immunotherapy. You might have difficulty answering the questions. But bear in mind: it is not meant as a test to judge whether you are "good" or "bad".

It was developed rather as an indicator for health professionals to gauge the need to deliver support when informing you about the disease.

Please read each question and tick only one answer.

Please read the following questions and tick the one answer in each group that you consider to be correct.

1. **Which one of the following statements about relapses is correct?**
   - Frequent relapses predict a faster worsening of impairment in the future, whenever they occur in the course of MS.
   - Frequent relapses during the first 2 years of the disease predict a faster worsening of impairment in the future.
   - If there are fewer relapses during the course of the disease it is a sign of improvement of the disease.
   - Severe relapses in any disease phase point to a faster worsening of impairment in the future.

2. **Which one of the following statements about MRI is correct?**
   - A patient's impairment can be determined by the MR image.
   - Contrast medium (gadolinium) enhancement visible on the MRI is a sign of active inflammation.
   - All MS patients should have a MRI done at least once a year.
   - Inflamed areas on the MRI (white spots) indicate destruction of nerve sheaths and nerve cells.

3. **Which one of the following statements about MS types is correct?**
   - When a MS diagnosis is made the disease course can be determined as well.
   - The switch from a relapsing to a chronic progressive course can be determined only in retrospect.
   - Very few MS patients have a relapsing MS course from onset.
   - The disease course of MS is not relevant for treatment decisions.

4. **Which one of the following statements about MS types is correct?**
   - Up to 30 out of 100 MS patients will remain without relevant impairments even after 20 years with MS (benign MS).
   - There is no such thing as benign MS.
   - Sooner or later all MS patients develop clearly noticeable, lasting impairments.
   - The development of impairments in MS does not depend on the disease type (relapsing or progressive).

5. **Which one of the following statements about the long-term course of MS is <u>correct</u>?**
   Studies carried out on MS patients who have never received immunotherapy show that after 15 years walking ability was almost unrestricted in…
   - approximately 90 out of 100 patients.
   - approximately 70 out of 100 patients.
   - approximately 50 out of 100 patients.
   - approximately 20 out of 100 patients.

6. **Which one of the following statements about the EDSS scale is <u>correct</u>?**
   - From the EDSS scale one can identify all relevant impairments in a patient.
   - EDSS scores from 4,0 to 7,0 are predominantly determined by the distance that patients can walk.
   - Increases in impairments are always reflected by increases in the EDSS.
   - Changes in vision and cognitive ability are assessed well by the EDSS scale.

7. **Which one of the following statements is <u>correct</u>?**
   A double-blind, randomised, placebo-controlled trial is…
   - a trial in which a new drug is tested against an old one.
   - a trial in which a drug is tested against a dummy drug (placebo). The patients are randomly assigned to receive the drug or the placebo. Neither doctor nor patient knows who gets which substance.
   - a trial in which a drug is tested against a placebo. The patients are randomly assigned to receive the drug or the placebo. The study physicians are informed about which substance is given to their patients.
   - a trial in which patients with their eyes blindfolded twice try out different drugs.

8. **The following three questions concern stability of impairment in trials on interferons in MS (8a, 8b, 8c). Please answer all three questions.**

   a) **Which of the following statements on the results of placebo treatment is <u>correct</u>?**
      Stability of MS when taking placebo:
      Imagine 100 patients with relapsing MS who all have 2 relapses per year. How many of these 100 patients can expect their level of impairment to remain stable on treatment with placebo within the next 2 years?
      - about 15 of those 100
      - about 25 of those 100
      - about 40 of those 100
      - about 70 of those 100
      - about 80 of those 100

   b) **Which one of the following statements about the results of interferon treatment is <u>correct</u>?**
      Stability of MS when taking interferon:
      Imagine 100 patients with relapsing MS who all have 2 relapses per year. How many of these 100 patients can expect their level of impairment to remain stable on treatment with interferon within the next 2 years?
      - about 15 of those 100
      - about 25 of those 100
      - about 40 of those 100
      - about 70 of those 100
      - about 80 of those 100

   c) **Which one of the following statements about treatment with interferon versus placebo is <u>correct</u>?**
      In answer to question 8a you stated how many of the 100 patients will remain stable without

therapy within the next 2 years. Now, how many **more** patients will remain stable as a result of interferon therapy (i.e. **in addition** to those who will remain stable without therapy)?

- about 10 of those 100
- about 25 of those 100
- about 45 of those 100
- about 55 of those 100
- about 65 of those 100

9. Which one of the following statements about therapy of different MS types is correct?

- There are currently no trials proving the effectiveness of treatments for patients with the first signs and symptoms of MS.
- There are currently no trials proving the effectiveness of treatments for patients with relapsing MS.
- There are currently no trials proving the effectiveness of treatments for patients with secondary progressive MS.
- There are currently no trials proving the effectiveness of treatments for patients with primary progressive MS.

10. Which one of the following statements concerning Copaxone® (Glatiramer acetate) is correct?

- The effectiveness of Copaxone® for reducing relapse rates is comparable to that of interferons.
- The effectiveness of Copaxone® for reducing relapse rates is better than that of interferons
- The effectiveness of Copaxone® for reducing relapse rates is worse than that of interferons.
- It is not possible to compare the effectiveness of Copaxone® and interferons for reducing relapse rates.

11. Which one of the following statements about flu-like symptoms, a side-effect of interferons, is correct?

- All MS patients will experience flu-like symptoms at least once at some stage of interferon treatment.
- Flu-like symptoms appear only at the beginning of interferon treatment.
- Approximately 50 out of 100 MS patients will experience flu-like symptoms at the beginning of interferon treatment.
- Approximately 10 out of 100 MS patients will experience flu-like symptoms at the beginning of interferon treatment.

12. Which one of the following statements about MS therapies with tablets is correct?

- Gilenya® (Fingolimod) is more effective than Tysabri® (Natalizumab).
- Gilenya® (Fingolimod) has hardly any side-effects.
- The efficacy of Tecfidera® (Dimethylumarat) is similar to that of the interferons.
- Aubagio® (Teriflunomide) is more effective than interferons.

13. Which one of the following statements about Tysabri® (Natalizumab) is correct?

- If treated with Tysabri® for 2 years approximately 40 out of 100 patients with relapsing MS do not have an increase in impairment because of the drug.
- More than 50 out of 100 patients suffer side-effects that come on suddenly as a result of treatment with Tysabri®.
- Approximately 3 out of 1000 patients who are treated with Tysabri® suffer a severe viral brain infection (Progressive Multifocal Leukoencephalopathy/PML).
- In addition to interferons, Tysabri® is a first-choice treatment for secondary progressive MS.

14. Which of the following statements concerning pregnancy and MS are correct?

- The relapse rate increases during pregnancy.

- Contraception is mandatory during any MS treatment.
- One out of 50 children with one parent affected by MS will get the disease as well.
- Breast feeding increases the risk of relapses.

15. Which of the following statements concerning complementary medicine and nutritional supplements is <u>correct</u>?

- Studies have shown that enzyme therapy reduces relapse rates.
- Studies have shown that polyunsaturated acids (e.g. fish oil, evening primrose oil) slow down disease progression.
- There are no convincing studies showing that complementary medicine or nutritional supplements influence the disease activity in MS.
- Studies have shown that vitamin D reduces relapse rates.

Now, for the following statements please tick the <u>one</u> answer that you consider to be <u>wrong.</u>

16. Which one of the following statements concerning diagnosis is <u>wrong</u>?

- MS diagnosis can be confirmed if typical symptoms and characteristic MRI findings are seen simultaneously and a further MRI made shortly afterwards provides evidence of new inflamed areas.
- In most cases MS can only be diagnosed after the disease has run its course for a while.
- Sometimes it can be difficult to diagnose MS beyond all doubt.
- MS can be diagnosed solely on the basis of antibodies in the cerebrospinal fluid that are only found in MS.

17. Which one of the following statements about relapses is <u>wrong</u>?

- Relapses are new symptoms that develop within days or weeks.
- Relapses are old symptoms that flare up for only a few hours.
- Relapses are intensified old symptoms or new symptoms that last for at least 24 hours.
- It can sometimes be difficult to distinguish relapses from daily fluctuations in MS symptoms.

18. Which one of the following statements about MS therapies is <u>wrong</u>?

- MS therapies aim to cure the disease.
- MS therapies work best in cases of relapsing MS.
- MS therapies can slow down disease progression.
- MS therapies can reduce the frequency of relapses.

19. Which one of the following statements about drugs for immunotherapy is <u>wrong</u>?

- Mitoxantrone may be used for the treatment of relapsing MS.
- Some interferon medications have been approved for the treatment of secondary progressive MS.
- Tysabri® (Natalizumab) has been approved for the treatment of relapsing MS.
- Gilenya® (Fingolimod) has been approved for the treatment of primary and secondary MS.

Source of RIKNO: HEESEN, C., KASPER, J., FISCHER, K., KÖPKE, S., RAHN, A., BACKHUS, I., POETTGEN, J., VAHTER, L., DRULOVIC, J., VAN NUNEN, A., BECKMANN, Y., LIETHMANN, K., GIORDANO, A., FULCHER, G., SOLARI, A. & AUTO, M. S. G. 2015b. Risk Knowledge in Relapsing Multiple Sclerosis (RIKNO 1.0) - Development of an Outcome Instrument for Educational Interventions. PLoS ONE, 10, e0138364.

Appendix D: MS-DOUBT study interviews script

You recorded having high/no decisional conflict (say as applicable to participant) in the questionnaires that you filled out recently at your clinic appointment, can you elaborate on why this is?

Tell me your story in your own words from the beginning – MS diagnosis onwards...' (chronology)

How do you approach decisions outside of healthcare?

Can you describe the MS services that you use and how regularly eg. hospital, specialist, online resources?

In what ways can information about treatments be challenging to understand or interpret?

Who would you describe as the most influential parties in your life and what influences(s) do they exert?

Can you describe a perceived outcome (or outcomes) that differed from the actual outcome of any treatments that you've received?

How has your approach to treatment priorities changed over time?

How would you describe the clinical trial experience versus standard NHS care?

In what ways are the treatment choices you make today informed by past experience?

How do you feel decisional conflict, with reference to treatment, may be resolved? OR

Have you experienced decisional conflict in the past and how did you resolve it?

How might support for patients with reference to treatments be improved at Imperial?

Have there been points in your life where you have felt more confident about making a decision?

As someone who lives with MS, how have your life priorities changed over time?

What is your treatment priority today/now?

Appendix E: Permissions

CPS Instrument

From: Solari Alessandra [mailto:Alessandra.Solari@istituto-besta.it]

Sent: 05 November 2019 11:20

To: Wilkie, David D <d.wilkie@imperial.ac.uk>

Subject: R: CPS figure

Sure!

A

Dr. Alessandra Solari
Unit of Neuroepidemiology
Fondazione IRCCS Istituto Neurologico Carlo Besta
via Celoria 11, 20133 Milan – Italy
tel: +39 02 2394 4664 4660
Skype: alessandra.solari2019@gmail.com
https://orcid.org/0000-0001-9930-7579

Da: Wilkie, David D <d.wilkie@imperial.ac.uk>

Inviato: martedì 5 novembre 2019 11:17

A: Solari Alessandra <Alessandra.Solari@istituto-besta.it>

Oggetto: CPS figure

Hi Alessandra

Do I have your permission to use the CPS figure attached in my thesis?

Thanks

SF-36v2 (requested)

From: Wilkie, David D

Sent: 23 March 2020 14:15

To: Lynda LaPlante <llaplante@qualitymetric.com>; Lori Jovin <ljovin@qualitymetric.com>

Subject: Re: PAID Optum Invoice SI045275 - AMENDMENT QM043609 for Software Upgrade and Key under Imperial College London License QM039454 - OPTUM #CT162248 OP067725

Dear Lori

I hope you can help.

Is it possible to include a copy of the SF-36v2 in the appendix of my PhD thesis?

Thank you in advance
David Wilkie
Imperial College London

PAM instrument

From: patientactivation (NHS ENGLAND & NHS IMPROVEMENT - X24) <ENGLAND.patientactivation@nhs.net>
Sent: 26 March 2020 15:12
To: Wilkie, David D <d.wilkie@imperial.ac.uk>
Subject: RE: PAM query

Hi David,

Yes this is fine and good luck with your work.

Kind Regards

Charlotte Cookson
Project Support, Personalised Care- Supported Self Management

Strategy and Innovation Directorate, NHS England NHS England and NHS Improvement, Quarry House, 4th Floor, Quarry Hill, Leeds, LS2 7UE

✉:Charlotte.Cookson1@nhs.net I☎: 07876 851908 |

From: Wilkie, David D <d.wilkie@imperial.ac.uk>

Sent: 23 March 2020 14:05

To: patientactivation (NHS ENGLAND & NHS IMPROVEMENT - X24) <ENGLAND.patientactivation@nhs.net>

Subject: PAM query

To whom it may concern

I have previously obtained a PAM licence to use PAM in my research into an MS population. Am I able to provide a copy of the instrument in the appendix of my PhD thesis so readers know to what I am referring?

Thank you in advance

David Wilkie

Doctoral Student

Imperial College London

From: Info [mailto:info@insigniahealth.com]
Sent: 31 October 2019 17:23
To: Wilkie, David D <d.wilkie@imperial.ac.uk>
Cc: Info <info@insigniahealth.com>
Subject: RE: General Inquiry to Insignia Health

Hi David,

Thanks for your inquiry and request for permission to use the PAM Levels graphic. You have full permission from Insignia Health to use the image in your thesis. See attached PNG (lower resolution) and EPS (higher res) versions.

Thanks,

Jim

Jim Honish
Sr. Director, Marketing
jhonish@insigniahealth.com

From: Support UK [mailto:supportUK@insigniahealth.com]
Sent: 24 March 2020 17:12
To: Wilkie, David D <d.wilkie@imperial.ac.uk>
Subject: RE: PAM query

Hi David,

That's absolutely fine.

Kind regards

Naomi

Naomi Cunningham-Dexter
UK Account Director
07769587345
ncunningham@insigniahealth.com

From: Wilkie, David D <d.wilkie@imperial.ac.uk>
Sent: 23 March 2020 14:21
To: Support UK <supportUK@insigniahealth.com>
Subject: re: PAM query

To whom it may concern

I have previously obtained a PAM licence to use PAM in my research into an MS population. Am I able to provide a copy of the instrument in the appendix of my PhD thesis so readers know to what I am referring?

Thank you in advance

David Wilkie

Doctoral Student
Imperial College London

SDM-Q-9 / SDM-Q-9-DOC

David Wilkie

Apr 21, 2016

Dear Isabelle,

I am a researcher based at Imperial College London and I am currently completing a PhD looking at treatment decision-making in MS. I have read your work on the SDM-Q-9 with interest. Do you know if this is free to use as part of my own research? In addition, the adapted doctor's version of the same document? Thank you for your help.

Isabelle Scholl to you

Aug 1, 2016

Hello David,
thanks for your request and apologies for my late reply.
You can use both the patient and physician version free of charge for research purposes, as long as you cite the two respective papers.
All the best with your work
Isabelle

Co-author permission(s): Professor R Nicholas and A Solari for chapter 2 and 3 content and use of RIKNO and MSKQ

From: Solari Alessandra [mailto:Alessandra.Solari@istituto-besta.it]

Sent: 23 March 2020 16:28

To: Wilkie, David D <d.wilkie@imperial.ac.uk>

Subject: Re: a couple of questions

Dear David, I'm well and I hope that things will be smoother in the UK. Regarding your points, my answer is YES on all of them.

Best wishes!

Alessandra

Da: Wilkie, David D <d.wilkie@imperial.ac.uk>

Inviato: Monday, March 23, 2020 5:12:21 PM

A: Solari Alessandra <Alessandra.Solari@istituto-besta.it>

Oggetto: a couple of questions

Dear Alessandra

I hope you are keeping well? The situation in Italy has been shocking to watch and the UK is on the same trajectory, albeit a week or two behind. Please take care.

In other news I am now in the final week before I submit the thesis and I would like to kindly ask if you are ok with me using the content for chapter 3 referencing myself as the lead author as it is currently being reviewed by the MSJ. This is the MS-DOUBT study content recently submitted for your review.

In addition, am I able to include the MSKQ and RIKNO in their entireties in the appendix section?

Thank you in advance and very best wishes Alessandra

David

From: Nicholas, Richard

Sent: 23 March 2020 17:39

To: Wilkie, David D <d.wilkie@imperial.ac.uk>

Subject: Re: quick question

Yes ok

On 23 Mar 2020, at 16:19, Wilkie, David D <d.wilkie@imperial.ac.uk> wrote:

Hi Richard

As below, I'm sorry to bother you with everyone going on, but as a co-author on the recent MSJ/MS-DOUBT paper, I need written confirmation that you are ok for me to use chapter 3 as written?

Thanks in advance

David

From: Nicholas, Richard

Sent: 03 November 2019 21:33

To: Wilkie, David D <d.wilkie@imperial.ac.uk>

Subject: Re: quick question

no problem to use the content as required r

From: Wilkie, David D <d.wilkie@imperial.ac.uk>

Sent: 03 November 2019 19:03

To: Nicholas, Richard <r.nicholas@imperial.ac.uk>

Subject: Re: quick question

Hi Richard,
I need on record that you are happy – as Alessandra is below – for me to use the paper content that we have discussed? I am happy to attribute aspects of it to you as a co-author or I will use the content in its entirety as it stands with myself as the author. I will of course adapt certain sections to fit the overall narrative, but I can't change the results for example.

Hopefully we can catch up this week? I have made good progress since you've been away.

Thanks

David

From: Solari Alessandra <Alessandra.Solari@istituto-besta.it>
Date: Sunday, 3 November 2019 at 16:05
To: "Wilkie, David D" <d.wilkie@imperial.ac.uk>
Subject: R: A few questions

Dear David:
Thank you for your email. My answers below (bold text). Regarding additional papers of potential interest, I have a few references:

- Synnot AJ, Hawkins M, Merner BA, Summers MP, Filippini G, Osborne RH, Shapland SDP, Cherry CL, Stuckey R, Milne CA, Mosconi P, Colombo C, Hill SJ. Producing an evidence-based treatment information website in partnership with people affected by multiple sclerosis. Health Sci Rep. 2018 Mar 6;1(3):e24. doi: 10.1002/hsr2.24.
- Heesen C, Rahn AC. Guest Editorial: Shared Decision Making in Managing Multiple Sclerosis: Revisiting the Research Agenda. IInt J MS Care. 2018 Nov-Dec;20(6):v-vi. doi: 10.7224/1537-2073.2018-098.
- Oreja-Guevara C, Potra S, Bauer B, Centonze D, Giambastiani MP, Giovannoni G, Kesselring J, Langdon D, Morrow SA, Nouvet-Gire J, Pontaga M, Rieckmann P, Schippling S, Alexandri N, Shanahan J, Thompson H, Van Galen P, Vermersch P, Yeandle D. Joint Healthcare Professional and Patient Development of Communication Tools to Improve the Standard of MS Care. Adv Ther. 2019 Nov;36(11):3238-3252. doi: 10.1007/s12325-019-01071-9.
- Reen GK, Silber E, Langdon DW. Best Methods of Communicating Clinical Trial Data to Improve Understanding of Treatments for Patients with Multiple Sclerosis. Value Health. 2018 Jul;21(7):762-766. doi: 10.1016/j.jval.2017.12.015. Epub 2018 Feb 9.
- Reen GK, Silber E, Langdon DW. Interventions to support risk and benefit understanding of disease-modifying drugs in Multiple Sclerosis patients: A systematic review. Patient Educ Couns. 2017 Jun;100(6):1031-1048. doi: 10.1016/j.pec.2016.12.028. Epub 2016 Dec 28. Review.

Very best wishes
Alessandra

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tel: +39 02 2394 4664 4660
Skype: alessandra.solari2019@gmail.com
https://orcid.org/0000-0001-9930-7579
Da: Wilkie, David D <d.wilkie@imperial.ac.uk>
Inviato: domenica 3 novembre 2019 14:30
A: Solari Alessandra <Alessandra.Solari@istituto-besta.it>
Oggetto: FW: A few questions

In addition, any key papers you think it would be useful for me to review ahead of the viva would be warmly welcomed. **I will**

From: "Wilkie, David D" <d.wilkie@imperial.ac.uk>
Date: Sunday, 3 November 2019 at 11:59
To: Solari Alessandra <Alessandra.Solari@istituto-besta.it>
Subject: A few questions

Hi Alessandra

I hope you are well? It was good to catch up with you at ECTRIMS.

Just to update you, I have taken 4 weeks away to finish the thesis and I am now returning to various chapters including the original literature review. Do you know of any glaring omissions that I should add to the table (below) referencing decisional interventions in MS? I last reviewed this in 2014 and I am aware of the aids we have discussed in RIMS over the years, but it would be great if I could get your input. The interventions below had an emphasis on RCT delivery but I am open to others. **To my knowledge, your list is complete.**

Another question I have for you is whether you would be happy for me to adapt the paper we had published into a chapter? https://www.ncbi.nlm.nih.gov/pubmed/30834139 As you were a co-author, I would like to ask if you are happy for me to use it as my own work or if you would like to be referenced to elements of the paper? Richard is happy for me to use it as my own work and I have already adapted it further but obviously I want to credit you as relevant. **I'm happy too!**

As for the second paper on MS-DOUBT, this reached peer review (which is positive) but was ultimately declined by the publisher (BMJ). Again I would like to use this as my own work and adapt it into a chapter, but please let me know if you would like to be credited to aspects of the paper and I will reference you accordingly. Otherwise I will use it as my own. **Again, that's fine with me.** Once I have completed the thesis, the aim is to return to the paper with updates and resubmit – possibly to MSJ, with yourself and Richard as co-authors. **Thank you for that.**

Thank you for all of your help with this process

David

James Cook permission to use content (chapter 4/appendix items)

From: James Cook [mailto:jamescookdirect@gmail.com]
Sent: 25 November 2019 22:16
To: Wilkie, David D <d.wilkie@imperial.ac.uk>
Subject: Re: Film

Hi David,

I'm very well thanks, how have you been keeping?

Yes of course that's absolutely fine. Just make sure that no document has anyone's addresses or contact details on, but other than that by all means. I hope it's all going well?

Best,

James

On Mon, Nov 25, 2019 at 7:20 PM Wilkie, David D <d.wilkie@imperial.ac.uk> wrote:

Hi James

Are you keeping well? I hope all is grand.

I'm about 3 weeks away from finalising my thesis and I wanted to ask your permission if I could use the various pre-production materials e.g. storyboard in its entirety, casting sheet, outfits doc, etc. I will of course credit/reference you appropriately.

Best wishes,

David Wilkie

Appendix F: Film script

AUDIO DETAIL	VISUAL DETAIL
A1	V1
	Black screen with white caption: You Have MS: *What Now?*
A2	V2
Music *(tbc)* *Gentle sound of wind; birds chirping*	*Live-action (LA):* Close-up on a tree branch covered with leaves. The background is out of focus. The scene is vibrant with colour.
A3	V3
Music continues	*Sketch animation (SA):* Background scene emerges into focus revealing a sketched suburban house, a drive-way on which sits a car (side-view) and a well-kept front garden on which sits the tree from V1 and a child's slide and swings.
A4	V4
Music continues	*LA/SA:* A caucasian woman in her mid-thirties is dressed smartly for business. She is seen gesturing goodbye to people indoors who remain unseen as she leaves the main entrance of the suburban home from V3. She proceeds to walk down a clear and tidy driveway towards the car.
A5	V5
Music continues	*LA/SA:* The animated car (first seen in V2) on closer inspection looks to be in immaculate condition, sparkling and gleaming. The woman enters it then drives away.
A6	V6

Music continues	*SA:* The scene pans towards the exhaust pipe - via the immaculate framework of the car driving at speed without issue - to a close-up (CU) on fumes escaping.
A7	V7
Music continues	*SA:* Mid-shot of the fumes escaping further into the environment, back towards the house, garden and the tree.
A8	V8
Music continues	*SA:* CU of tree branches. The car fumes pass-by with no effect. The background is blurred-out.
A9	V9
Music continues	*LA/SA:* The background comes into focus and V3-7 scenes repeat to illustrate continuity of routine. There is variation ie. different outfit worn by the woman. There are scratches on the car's bodywork when the camera pans towards the tree for a second time.
A10	V10
Music continues	This time, V8 scene sees the fumes having an effect – some of the leaves are showing discolouration from vibrant green to yellowish-brown. A few fall and the camera tilts to follow one of them to the ground. Background out of focus throughout before coming back into focus where V3 repeats.
A11	V11
Music continues Sounds of engine faultering.	V4 plays out as before but this time the drive way is scattered with leaves but not enough to prevent the car from exiting. There is noticeable

	deterioration on the bodywork. The woman is busy on her phone, unaware of the deterioration.
A12	V12
Music continues	The woman enters the interior of the car. Once inside she examines the key – which has a crack in it. She puts it in the ignition and struggles to start the engine. It takes several attempts before it works.
A13	V13
Music continues	V6-7 scene plays out as before with additional footage showing the car with signs of wear and tear ie. minor scratches on the body, scuffing marks etc. It moves at reduced speed.
A14	V14
Music continues	V8 repeats but this time many of the leaves are discoloured and the fumes appear to be taking hold. The background is blurred out.
A15	V15
Music continues	V3 repeats but with diminished colour.
A16	V16
Music continues *A bang/popping sound is heard*	The woman looks at her watch and the scenes repeat as before. She places the key into the ignition but the car won't start. After several attempts the engine appears to start before a bang/popping sound is heard. She gets out of the car to investigate.
A17	V17
Music continues	The woman examines the car in more detail and notices wear-and-tear, seemingly for the first time acknowledging it. She glances at the driveway to find it covered in leaves and back at the house to see its once vibrant look has now diminished with cracks in the brickwork. Even if she wished to drive off, she would be unable

	to. She glances towards the tree to see it without leaves as they fall into her path.
A18	V18
Music continues	The woman goes to the car bonnet and opens it, observing the engine over-heating as copious smoke billows out at speed.
A19	V19
Music continues	We follow the smoke to the tree which is now enveloping it. Only a few leaves now remain. There is diminished colour throughout the scene. The camera zooms out of the scene from above before fading to black.
A20	V20
Music continues	From black, the scene comes back into focus and we zoom back into V19 before all the previous scenes reverse at speed up to V1. We pause briefly at V2 and V3 before we return to the opening caption (V1).

Appendix G – MS Film Casting Sheet

Multiple Sclerosis - "What Now?" Awareness Film

Casting

Devora Wilde

https://actors.mandy.com/uk/actor/profile/devora-wilde?show-file=1002074

Lisa Bridge

https://actors.mandy.com/uk/actor/profile/lisa-bridge?show-file=1156437

Lara Lemon

https://actors.mandy.com/uk/actor/profile/lara-lemon?show-file=1098620

Nicola Evans

https://actors.mandy.com/uk/actor/profile/nicole-evans-2?show-file=978232

Appendix H - MS Film protagonist wardrobe idea board

Appendix I – MS Film stylistic moodboard

Appendix J - Snapshot of the prototype website