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Title page

Title: Impact of Communication on First Treatment Decisions in People with Relapsing-Remitting Multiple Sclerosis

Authors' names and affiliations:

Manzano, Ana[a]; Eskytė, Ieva[b]; Ford, Helen L[c]; Bekker, Hilary[d]; Potrata, Barbara[e]; Chataway, Jeremy[f]; Schmierer, Klaus[g]; Pepper, George[h]; Meads, David[d]; Webb, Edward JD[d]; Pavitt, Sue H[i]

[a]School of Sociology & Social Policy, University of Leeds, Leeds, United Kingdom

[b] School of Law, University of Leeds, Leeds, United Kingdom

[c]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

[d]Leeds Institute for Health Science, University of Leeds, Leeds, United Kingdom

[e]Independent Consultant, Rotterdam, The Netherlands

[f]Department of Neuroinflammation, UCL Institute of Neurology, University College London , London, United Kingdom

[g]Blizard Institute (Neuroscience), Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London, United Kingdom

[h]Shift.ms, Leeds, United Kingdom

[i]School of Dentistry, University of Leeds, Leeds, United Kingdom

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Corresponding author: Dr Ana Manzano, School of Sociology & Social Policy, Room 11.20 Social Sciences Building, University of Leeds, Leeds LS2 9JT, United Kingdom

Email address: a.manzano@leeds.ac.uk

Telephone/FAX: 00441133431290

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Abstract

Objective: Disease-Modifying Treatments (DMTs) have contributed to a new clinical landscape for people with relapsing-remitting multiple sclerosis (pwRRMS). A challenge for services is how to support DMT decisions with changing clinical evidence, and differing treatment goals. This article investigates how pwRRMS weigh up the pros and cons of DMTs by examining how communication at the point of diagnosis is related to DMT decisions.

Methods: 30 semi-structured interviews with pwRRMS in England were conducted using a theoretical purposive sampling strategy and analysed using the thematic approach to answer: How does communication about RRMS during diagnosis influence decisions about when and which DMT to choose?

Results: Three meta-themes were identified: a) communication context; b) delayed communication and hope for people with “non-active” RRMS at diagnosis; c) people with “active” RRMS at diagnosis: Conflated, generic, selective and simplified information

Conclusion: At the time of diagnosis, patient–physician interactions are characterised by emotions and information complexity. Clinical, social and psychological DMT filtering mechanisms are activated during first decisions. Personalised evidence is needed to make informed decisions.

Practice Implications: Patient decision aids should consider first and consecutive decisions and should not encourage a false sense of large choices that could add to decision anxiety.

Impact of Communication on First Treatment Decisions in People with Relapsing-Remitting Multiple Sclerosis

1. Introduction

Rapid advances in brain imaging and Disease-Modifying Treatments (DMTs) have contributed to a new clinical landscape in the diagnosis, treatment and care for people with relapsing-remitting multiple sclerosis (pwRRMS) [1, 2]. These advances mean a) more people are diagnosed with RRMS earlier in their lifespan; b) more treatments are available to manage symptoms and modify disease mechanisms; c) decision-making about how best to manage RRMS to fit in with people's lives is more complex [3] with immature evidence on the long-term consequences of DMTs [4, 5] and on effectiveness of treatment strategies (induction versus escalation) [6].

A challenge for services is how to best support people's management of their RRMS with changing clinical evidence and disease state, and differing goals for treatment planning. Evidence suggests patients do not receive adequate information from health care providers about DMTs [7] with advocacy groups requesting resources such as decisions aids for guidance [8]. Physicians' competency to communicate DMTs risks and benefits needs support [9]. Few studies have assessed patient-involvement interventions in MS care [10], and it is unclear how well usual practice meets these complex communication needs [11].

This article presents findings from a study aiming to investigate how pwRRMS weigh up the pros and cons of DMTs. We examine how communication at the point of diagnosis is related to DMT decisions. However, during pwRRMS' disease and

treatment course, experiences of communication change. How these changes impact future treatment decisions is described elsewhere [12].

2. Methods

Little is known about DMT decision-making from the perspective of pwRRMS and, qualitative methods are recommended for exploring experiences, meaning and perspectives from the standpoint of the participants [13, 14]. A qualitative study of 30 semi-structured interviews with pwRRMS was performed to obtain in-depth understanding of people's experiences of choosing DMTs from when they were first diagnosed until the day of the interview. This includes identification of the main factors in starting, stopping, or switching DMT, which ones they prefer and why. In this paper we report findings on reasons to start and which ones to choose as their first DMT sometimes -but not always- shortly after diagnosis. This qualitative study was part of a project to develop a patient centre decision aid [15], which included evidence of stakeholders needs identified through systematic reviews [16. 17], interview study, and surveys using discrete choice experiment methods.

Participant eligibility criteria were: Clinician confirmed diagnosis of RRMS; aged 18+; written informed consent. We asked MS specialist neurologists in a MS referral centre in a large teaching hospital in the north of England (United Kingdom) to identify people meeting our study criteria. Patients were approached by a research nurse and once consent was obtained, they were contacted by a qualitative researcher (IE) who arranged a convenient place and time for the interview. There

were 42 patients identified, 30 took part, nine declined to participate due to logistical issues (work commitments or lifestyle); and we were unable to contact three people. A theoretical purposive sampling strategy [18] was used to obtain a varied sample in terms of DMT experience, in that we sought participants with diverse experiences of taking DMT (treatment naïve, experience with specific DMTs, people who decided to switch or stop DMTs), since these categories had been identified as relevant for the decision-making process in the literature. Even though analysis was guided by this knowledge, it was open to identify any potential new and emerging themes. For example, after analysing data from the first ten interviews, significant factors in DMT decision-making were identified that drove subsequent recruitment eligibility criteria to further consolidate our initial findings: women of fertile age; experience with DMTs with risk of progressive multifocal leukoencephalopathy (PML)[1]; within one year of diagnosis; decided not to start DMT at the time of study entry; in full-time employment.

Interviews lasting between 45-90 min were conducted by an experienced qualitative researcher (IE) and were face to face (n=22) -in the participants' homes or their preferred venue (public space, private room in the hospital, etc.), or by phone (n=8) (Table 1). Topic guides (Table 2) were used which were informed by a systematic review [17], a critical interpretive synthesis [16], three focus groups (FG) and one dyadic interview [19] with pwRRMS. Two of the FG (n=7 and n=5) were with health care staff, including MS nurses and neurologists one small FG with pwRRMS (n=3).

[Insert Table 1 here]

[1] A life-threatening viral disease.

Interviews were audio-recorded with participants' permission and all data was safely stored and anonymised, transcribed verbatim and analysed using a thematic analytical strategy [20] consisting of four interconnected steps:

a) One qualitative researcher (IE) read verbatim transcripts to identify initial themes, guided by a flexible coding strategy based on our previous work. b) Detailed sub-categories to illustrate these themes were created and coded using NVivo (©QSR) International qualitative analysis software by IE, AM. c) These sub-themes were grouped into three broader categories or meta themes. This was done- by cross-referencing individual accounts with the entire data set and the rest of the themes. d) Meta-themes were refined through regular discussions with the wider research team (BP, HB, HF, SP), which included a pwRRMS (GP). The aim of the analysis strategy was to understand what is important in making decisions about treatments and when to start by examining: How does communication about RRMS during the diagnosis influence decisions about when and which DMT to choose?

Ethical approval was obtained from the NHS Health Research Authority (IRAS: 199646).

[Insert Table 2 here]

3. Results

Three meta-themes were identified: communication context; "non-active" RRMS at diagnosis; and active RRMS at diagnosis.

3.1 The Communication Context: Emotions, Clinical Pathways and Evidence

People's experiences of the confirmation of diagnosis were heterogeneous, but there was a clear homogenous pattern in post-diagnosis emotional state: distress, shock, anger, stigma, sadness and fear. There was also relief for some, which relates to ending uncertainty caused by delayed diagnosis [21-23], often with previous misdiagnoses including neurological, psychiatric and non-MS related eye disorders. People often related their emotional states to their choices about starting treatment. Adaline (aged 34) was informed of the diagnosis over the phone six years ago:

> *"Not starting treatment was probably partly to do with the fact I didn't want to accept I had MS. That's a massive thing when you first get diagnosed cause when I was first diagnosed I even heard them wrong on the phone. I heard that I didn't have MS and that everything was wonderful but actually they were telling me that I did have MS. I completely heard something different. It just seemed a bit too real and I think I just didn't wanna go on treatment."*

Within this emotional context, several incidents of ineffective practice in diagnosis communication were reported, with people having to 'guess' they had MS, being told over the phone, or finding out in referral letters. This was not the case for all participants with some recalling more effective communication practices. Although the possibility of recall bias should be taken into consideration, at the point of diagnosis people often reported limited in-depth conversations about RRMS, which were sometimes delayed until follow-up appointments. These experiences were equally observed in people diagnosed decades ago and recently. Time gaps between diagnosis and follow-up appointments magnified negative emotions about

RRMS and clinical pathways. Eleonore (age 27) was diagnosed three months before the interview:

> *"So somebody just told me I had MS and then told me you will have to wait three months to understand what it is, no booklet, nothing"*

People employed their own strategies to find additional information about RRMS with mixed success. Information was pursued online with a small number of participants also paying privately for consultations. People felt overwhelmed by information but unable to trust or interpret it:

> *"A lot of people, when you get diagnosed, 'well my friend's got MS', or, 'I was reading the paper the other day and there was a story about this drug'…People are trying to be nice and give you positive stories but to a degree you are just overwhelmed with all this information." (Sam, age 39)*

RRMS heterogeneity and how this affected DMT efficacy evidence was clearly communicated to people. This uncertainty framed the decision-making process, as Debbie (age 32) who stayed without medication for ten years recalled:

> *"I find that uncertainty very difficult too, I found that a big part in deciding whether to take the drugs or not. Whether it was like taking a gamble of whether I'd be alright without it."*

Recently diagnosed people had the added complexity that in current clinical pathways, diagnosis and treatment decisions are closer and can coincide [24]. In

England to be prescribed a DMT, people need to meet clinical eligibility criteria (Table 3). This process creates two distinct communication experiences: 1) People categorised as having “inactive” RRMS; 2) People categorised with active RRMS meeting funding criteria to initiate DMT immediately.

[Insert Table 3 here]

3.2 “Inactive” RRMS at Diagnosis: Delayed Communication and Hope

Standardized definitions for MS clinical courses were established in 1996, revised in 2013 [25, 26], and in England inform clinical guidelines [27] and funding eligibility criteria [28]. The Lublin revision considered disease “activity” frequency as a modifier of the basic clinical course phenotype in RRMS (Table 3) but these phenotypes remain contested. During their life, pwRRMS may experience different levels of disease activity, and neurologists cannot predict when or how these may happen. Neurologists working in England perceive National Institute for Health and Care Excellence (NICE) prescribing guidelines as mandatory [29] and people who do not have active RRMS are not-eligible for DMTs. In our study those who did not meet DMT funding criteria when they were first diagnosed experienced reduced and delayed communication about how RRMS transitions through different stages of activity.

The distinction between inactive/active RRMS implicitly contributed to the hope that not meeting funding eligibility criteria equated to a form of “non-RRMS” which prevented people from initiating conversations not only about DMTs but also about RRMS clinical course. The periods of time when people did not meet funding criteria varied between a few months and years or decades. Participants waited in the hope

that their RRMS did not advance, but they all described some level of “disrupted normality” [30]. People often did not passively wait for RRMS to advance, using non-biochemical self-management strategies such as diets and exercise routines based on beliefs associated with decreasing stress and relapses.

The timeframe between the evidence of DMT eligibility (clinically relevant frequent relapses [2]) and this being brought to the attention of medical professionals is mainly dependent on patients self-reporting symptoms. People frequently entered an active RRMS phase without reporting new symptoms because of a combination of individual and institutional interrelated factors (Table 4). This can be illustrated by Elisa’s (aged 33) case who stayed without treatment for four years. She only started on Natalizumab (immune blocking DMT, administer monthly in hospital) when her mobility significantly reduced:

> *“I didn’t think I needed treatment because … I didn’t feel too bad. Like I say I went downhill quite quickly. But I didn’t phone my nurse or owt like that because I didn’t notice it as such with it being a gradual decline. But maybe if I’d have known a bit more.”*

[Insert Table 4 here]

Some people in this group interpreted not being eligible for treatment as a positive sign because they hoped that this meant that their RRMS was not advancing. Others, who often experienced a more intrusive “non-eligible” fluctuation during the waiting period explained that when they tried to initiate conversations about DMTs, often doctors were not “open to discuss treatment” just yet.

When criteria were met, this was interpreted as a sign of their RRMS advancing but also as an offer that could not be refused. Debbie (aged 32) who finally qualified after having two relapses ten years after diagnosis, summarised this:

> *"I thought now that the NICE guidelines were saying that I'd qualified, that made me think, 'Oh, I must be getting worse…to the point where they will do something to help me'. And then I couldn't live with the not taking treatment and not knowing if I had taken the treatment, if I'd have been better."*

In summary, people with "inactive" RRMS waited in fear of their RRMS advancing, but communication encounters about RRMS and DMTs were few and delayed. Although a small proportion of pwRRMS continue to have inactive RRMS during their lifespan, the majority have fluctuating levels of activity (relapses and periods of remission) and will transition to secondary progressive MS [31].

3.3 "Active" RRMS at Diagnosis: Conflated, Generic, Selective and Simplified Information

People whose RRMS met disease activity funding eligibility criteria [2] at diagnosis mainly experienced communication about treatments conflated with diagnosis information. For some people, like Catrina (aged 38, diagnosed two years ago), DMT information was encountered unintentionally (in referral letters, leaflets, etc.) or intentionally (searching online) even before diagnosis disclosure:

> *"I'd been to see my neurologist with the funny eye thing and I was supposed to have a review appointment with someone else. And I got a letter from the*

hospital saying, 'You have been transferred across to Dr X clinic which is a DMT clinic'. I was like, 'what the hell's DMT?' So I looked up DMT on the internet and it was like, 'Oh, it's disease modifying therapy. Okay so it probably is MS then' […]. So my next appointment will be telling me that, and discussing these therapies."

People in this group were confronted with the initial decision to take treatment and which one to take while the natural emotional responses to diagnosis were very raw and knowledge about RRMS very poor. This is significant because conversations about whether to start treatment cannot be disentangled from which DMTs are available to each person and this availability is also related to RRMS phases and disease prognosis.

In our sample, it was apparent that the new drug landscape for RRMS distinctly influenced communication practices, with a potential long list of DMTs being used during consultations (12 DMTs were available during data collection [15]). Neurologists normally introduced DMTs generic information, with MS nurses often dedicating more time to discuss specific details. Sometimes neurologists presented the full list of drugs without grouping or categorising them, which added to the fear of making the wrong decision. In these situations, people instinctively categorised DMTs by mode of administration since this was the only treatment attribute they could relate to:

"To be honest there was probably too many [DMTs]. I remember the big pull out leaflet that had them all on, and it was just, baffling really… I remember reading a table of pros and against, and it was quite confusing because there were too many. And some that were very similar in effectiveness. The

percentages and side effects, a lot of them were very similar, but they might've been injecting daily, once a month an IV injection." Suzie (aged 30, diagnosed seven years ago)

Often participants reported neurologists providing a narrow set of options informed by their clinical judgement around three criteria:

a) **Clinical incompatibility** with some of the DMTs on the list, assessed by medical history and blood test screening or likelihood of effectiveness. This discarding mechanism sometimes resulted in a significant reduction of available choices. For example, Alex (aged 50) who had been on Copaxone (daily self-injectable immune modulation DMT) for five years at the time of interview explained how he was only offered two DMTs:

"They looked at the blood test and said, 'there are two possibilities for you'. 'This is one and this is the other'."

b) **Treatment approach and funding**. Some DMTs were excluded at the point of diagnosis because *"you are not that bad yet"*. For example, only people categorised as having rapidly-evolving severe RRMS were offered immune reconstitution and immune blocking drugs, with the rest being presented with a reduced list of mainly immune modulation DMTs [32] (Table 5).

[Insert Table 5 here]

The conflation of treatment approach and funding seemed to generate feelings of privilege to the point that it seemed "immoral" to reject a DMT offer:

"I was lucky then that I was offered this treatment [Interferon, self-injectable immune modulation DMT] cause not everybody does. When I think back, that was why I did it, cause part of me partly felt, 'if I don't do it now I'll not get the opportunity again'. Especially if I don't have a relapse within a year cause that seemed to be criteria. Or you had to have so many relapses within a set period." (Rosa, aged 51, diagnosed three years ago).

c) **Clinical judgement and/or neurologist preference** were perceived as influencing the DMT offered. People often referred to the DMT "the doctor wanted me to take" or just said "they have put me on this treatment". These preferences were mostly presented using simplified and sometimes simplistic explanations about risk and efficiency rates, as Tom (aged 44) explained:

"The choice was presented to me as a recommendation that I was free to disagree with. But the way in which it was presented, it was: 'There's Interferon [self-injectable] which reduces relapse rates by a third. And then there's this neuro drug called Dimethyl Fumarate [tablet] which reduces relapse rates by about a half and you don't have to have injections.'"

Incidents of people disagreeing with recommendations were scarce but present. When people chose a different DMT than the one recommended, this choice was respected. Tamara (aged 22) chose Alemtuzumab (immune reconstitution DMT, two infusions in hospital, one over five days, and another one, a year later over three days) as her first DMT:

"My doctor actually tried to convince me to go on the Natalizumab (infusion at hospital, one half a day every four weeks). He said a lot of his patients who are on Natalizumab would never ever choose anything else. And I was like, 'No, I've made my decision'. Please don't try and change it now".

Participants acknowledged and often welcomed the need to have neurologists filtering options to support decisions given the uncertain and complex evidence. However, some filtering mechanisms, seemed to be informed by staff assumptions about DMT availability (funding criteria) and clinician personal preference.

People reflected on their reasons to start treatment which were mainly clinical (effectiveness) after having a relapse. People activated their own filtering mechanisms to choose which DMTs to take. These included a combination of social incompatibility (work, childcare), psychological factors (fears) with mode of administration and possible side effects. Suzie (aged 30) described how she chose her first DMT (Interferon, self-injectable) after rejecting Natalizumab (administered in hospital) because it was incompatible with childcare:

"I remember thinking that most of them had a similar percentage of success rate, so for me I suppose clinically that was all that really mattered. The side effects, there were good and bad to each of them. For me, it was more my personal life, like how safe are they around the children."

To be able to rule out a DMT, people needed information so they could be evaluated with their own social and personal values rather than attributes of treatments assumed to be important for their effectiveness. As one of our participants (Chandler, aged 27) noted, people are told "this will happen" rather than having meaningful

conversations about how DMTs attributes could impact in their life: “this will happen, how do you think this will affect you?”

4. Discussion and Conclusion

4.1 Discussion

This article illustrates how the growing complexity of RRMS diagnosis, treatment [33] and prognosis communication impacts people’s ability to make meaningful first decisions about DMT. These decisions are unique and different from those taken later on in the disease course about switching to a different DMT [12].

Despite the significant increase of DMT availability, uncertainty about effectiveness remained common [34]. The natural emotional state post RRMS diagnosis [9, 35, 36] was exacerbated by clinical pathways characterised by few, short, diverted, delayed, selective and generic communication encounters. On the whole, people’s knowledge needs about RRMS were not met and these are intrinsically related to DMT decisions. Patient–physician interactions at the time of diagnosis are characterised by stigma and fear, and information complexity. Disease course uncertainty and treatment benefits and risks add a greater emotional dimension. Within this context, quantity and quality of conversations were often perceived by pwRRMS as insufficient with information not being presented in a way that people could meaningfully interpret. These findings highlight the importance of physician communication when delivering diagnosis news, and how this is related to discussing prognosis and negotiating first treatment decisions.

Early treatment is now the recommended approach in RRMS [1, 37]. Too often, however, the necessary understanding of the disease impact and prognosis is not present in order to make informed choices. Physicians filtering mechanisms to support decisions were a mix of clinical and funding factors but patients filtered choices using a more complex combination of clinical and psycho-social factors. Furthermore, in RRMS, the definition of individual prognosis is problematic [33] but clinical and national funding criteria, though not static, are often categorised as clear cut. In England, the distinction between inactive and active RMS influenced the pwRRMS communication experience, creating two distinct groups based on disease activity, while the categorisation of what counts as activity is often based on patients reporting it. In our study, established clinical pathways to monitor activity in those who are not taking DMTs seemed to be lacking.

4.2 Conclusion

This study demonstrated how both pwRRMS and clinicians used different filtering mechanisms to reduce the number of DMTs available to them during the decision-making process. The limitations of this study are that it is based on people's recall of communication, which is not always an accurate reflection of the information given during diagnosis and decision-making. However, it indicates that there is a consistent theme around decision conflict that is sustained over time, and suggests that more support is needed to encourage discussions along care pathways.

4.3 Practice implications

Decision aids can be helpful in a) providing a memory prompt, b) presenting all options and consequences neutrally, c) guiding people to think about how to cope with the fluctuating and dynamic nature of MS, d) categorising facts about MS and treatment options in a way that is cognitively easier to assimilate in emotional situations, and e) enabling informed conversations with the clinical team to agree on choices that are best for pwRRMS at that time, but may change [15]. However, patient decision aids should allow for different types of decisions (first and consecutive) and should not encourage a false sense of large choices that could only add to decision anxiety. Evidence must be individualised for the patient [38] so they can personalise it and make informed decisions. This requires a strong clinician-patient relationship, which includes finding out what matters to people while allowing clinicians to exercise expert judgement. However, despite the institutional promotion of patient choice [39], optimal decisions require optimal circumstances and current clinical pathways and mechanical funding rules constrain this relationship and do not always encourage timely dialogue.

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