The potential of a novel cell-based therapy delivery implant in multiple sclerosis: an early health technology assessment

Thesis

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GENERAL INTRODUCTION

This thesis describes the early Health Technology Assessment (HTA) of a novel cell therapy delivery implant in multiple sclerosis (MS) patients. In this introduction, MS will be described, along with the current treatment options available, followed by introducing the cell-based optogenetics drug delivery implant. Furthermore, (early) HTA will be explained along with why early HTA is appropriate when developing a new mode of treatment administration.

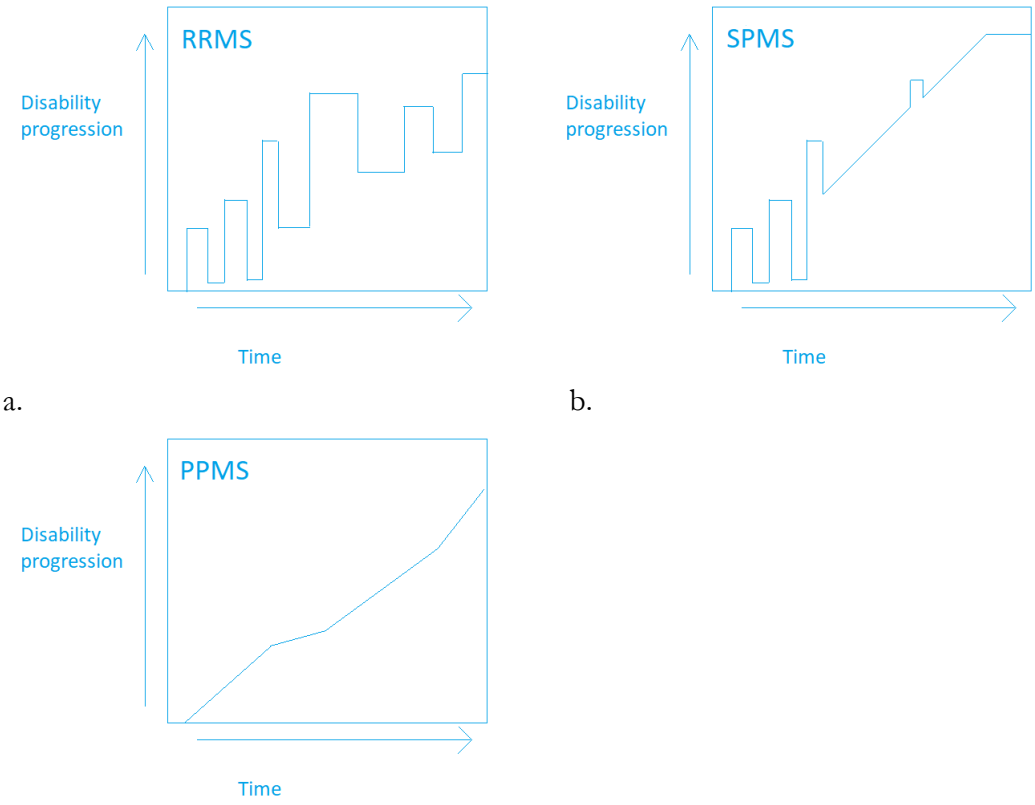
MULTIPLE SCLEROSIS

Multiple sclerosis is a chronic demyelinating disease of the central nervous system (CNS). It is a disease that primarily affects women, who are three times more likely to be affected than men, and persons are usually diagnosed between the ages of 20 and 40. There are almost 1.2 million persons in Europe with MS and a total of 2.8 million persons globally (1,2).

There are multiple types of MS (see Figure 1). The most prevalent type of MS is relapsing-remitting MS (RRMS), affecting 85-90% of patients. Persons with RRMS suffer from periods of neurological dysfunction, known as a relapse, alternating with periods of remission (3). A relapse is characterized by a patient-reported or objectively observed acute inflammatory demyelinating event of the CNS (without any signs of infection or fever) that lasts for at least 24 hours (4). A typical presentation of a relapse may be sensory problems (double vision, tingling) or physical dysfunction (asymmetric limb weakness, sexual dysfunction) (3). Ten to fifteen percent of persons with MS suffer from progressive neurological dysfunction without relapses (primary progressive MS: PPMS). Persons with RRMS may develop a progressive disease course (secondary progressive MS: SPMS). They no longer have relapses but do suffer from progressive neurological dysfunction (3). Furthermore, some persons only experience one clinical attack and are diagnosed with MS based on lesions found using magnetic resonance imaging (so-called dissemination in time and space: new lesions found on the follow-up magnetic resonance imaging (MRI) with a baseline scan to compare, or at least two typical MS lesions of the CNS) (3,4). These patients are diagnosed with a clinically isolated syndrome (CIS) and may later be diagnosed as clinically definite MS.

Disease severity can be measured using the validated Expanded Disability Status Scale (EDSS) instrument (5). This instrument should be administered by the (treating) physician and evaluates the functional systems of the CNS. The EDSS is an ordinal scale from 0 (no disability) to 10 (death due to MS) with 0.5 increments. Generally speaking, the disability can be subdivided into mild disability (EDSS 0-2.5), moderate disability (EDSS 3-5.5), and severe disability (≥6) (6). There are some criticisms, however, such as the instrument having limited reliability and is somewhat sensitive to changes in disease progression. Also, the scale properties have been criticized. Persons are classified with mild disability based on the neurological exam. Whereas, persons are classified with moderate disability based on walking ability, and persons with severe disability are classified as such due to handicaps (5). Nevertheless, the EDSS is frequently used in clinical trials and remains the only validated outcome measurement to determine disability (7).

Figure 1 The natural history progression of multiple sclerosis



Natural history progression for a) RRMS: relapsing-remitting multiple sclerosis, b) SPMS: secondary progressive multiple sclerosis, and c) PPMS: primary progressive multiple sclerosis.

Disease-modifying therapy

There is no cure for MS. Nevertheless, it is important to diagnose a person with MS as early as possible and start treatment soon (8). The first disease-modifying therapy (DMT) developed for MS was beta-interferon (INFβ), which was approved in Europe by the European Medicines Agency (EMA) and in the United States of America by the Food and Drug Administration (FDA) in 1995 and 1993, respectively (9). INFβ is a first-line DMT and is administered via injection. Other first-line DMTs are glatiramer acetate (GA, administered via injection), dimethyl fumarate (DMF), and teriflunomide, the latter two are taken orally. Patients may switch to another first or second-line therapy if they have a break-through of disease when on a first-line DMT, i.e. when the treatment is not effective enough. Persons may also switch DMT when the disease course becomes more progressive. Second-line treatments are fingolimod and cladribine (both taken orally), natalizumab (NTZ), ocrelizumab, and alemtuzumab (all three are given intravenously) (9,10). More recently, in 2020, ozanimod (oral therapy for patients RRMS) and siponimod (an oral therapy primarily for patients with SPMS) entered the market (11,12).

DMTs differ in efficacy, reducing relapse rate by 29%-55%, reducing disease progression by 12%-38%, or reducing MRI activity by 27%-85%. Second-line treatments are more effective than first-line DMTs. Furthermore, DMTs differ in their safety and tolerability profile. Common side effects are injection-site reactions, infusion reactions, and gastrointestinal symptoms, whereas serious adverse events include liver toxicity and progressive multifocal leukoencephalopathy (PML) (8). Persons with MS may find it difficult to choose amongst the treatment options. Therefore,

the physician should consider the patient characteristics, comorbidities, drug safety profile, disease severity and activity, and accessibility of the drug when informing the patient on DMT choices (10).

The safety and tolerability profile of DMTs can make MS very burdensome. Consequently, persons with MS aren't always 100% adherent to their treatment (13,14). Unfortunately, patients with lower adherence rates suffer from more relapses, more inpatient hospitalization, and higher MS-related healthcare utilization costs (13).

Quality of life and the economic burden of multiple sclerosis

Patients with MS have a lower quality of life (QOL) than persons in the general population (15–17) and other chronic diseases (18,19). Factors such as disease progression (15,20) and mental health disorders (such as depression and psychological distress) (20–22) reduce the QOL of MS patients. Depending on the disease severity the type of MS symptoms that affect QOL differ. For example, gait and balance problems have a negative effect on QOL for persons with RRMS. Whereas spasticity and bowel problems are the more prominent problems for persons with progressive MS (23).

The economic burden of MS is high. In Europe annual mean costs for persons with MS range from €22,800 up to €57,500 (2015 Euros, adjusted for purchasing power parity) depending on disease severity (24). The resources the money is spent on shifts with disease progression. In the early disease stages with mild severity the bulk of the costs are spent on DMTs. Later on, however, the majority of the costs are related to informal care and community services. Furthermore, productivity losses become more apparent in moderate and severe disease severity (24).

In the United States of America, a 128% increase in the number of DMT prescriptions, coinciding with a 633% increase in annual reimbursement of DMTs ($1.26 billion) was noted over a 10-year period from 2008-2018 in Medicaid-enrolled MS patients (insurance for low income persons in the USA) (25). Expenditures are likely to be even higher since these numbers do not represent the whole US MS patient population. Increases in the US expenditure costs can be attributed to increase in the number of DMTs available to patients and an increase in disease prevalence and life expectancy (25).

CELL-BASED OPTOGENETICS DRUG DELIVERY IMPLANT

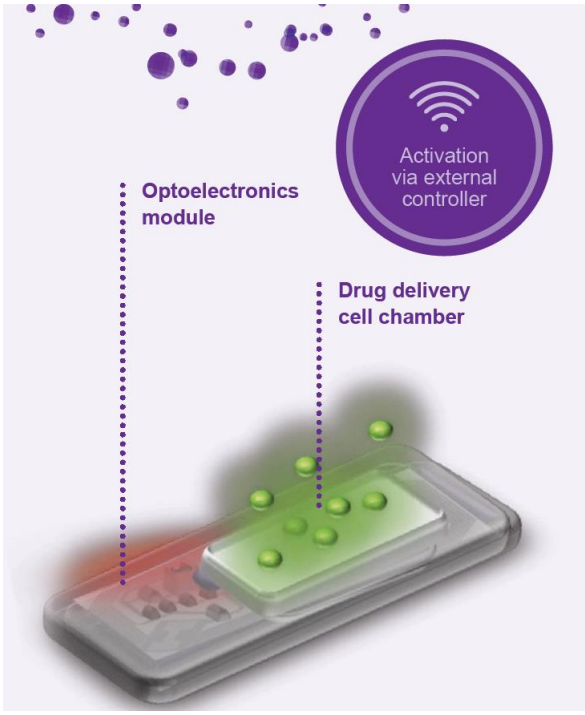
The abovementioned problems, such as burdensome side effects, non-adherence, lower QOL, and high healthcare costs seem to suggest that there may potentially be a gap to be filled in the treatment regimen given to patients. The Optogenerapy consortium jumped in to fill such a gap.

The Optogenerapy consortium aims to develop and demonstrate a wireless powered, cell-based optogenetics implantable device to administer INFβ to persons with MS (Figure 2). INFβ is a naturally accruing cytokine secreted by immune cells and it has an anti-inflammatory effect on the CNS (26). The cell-based implant is classified as a combined advanced therapy medicinal product (cATMP) that combines various technologies such as macro-encapsulation, electronics, and optogenetics. The implant contains genetically modified mammalian light-sensitive cells that are modified to release INFβ into the body via a semi-permeable membrane. This is made possible by an optogenetic interface to control the cellular behavior of the cells and is powered by a wireless belt (27).

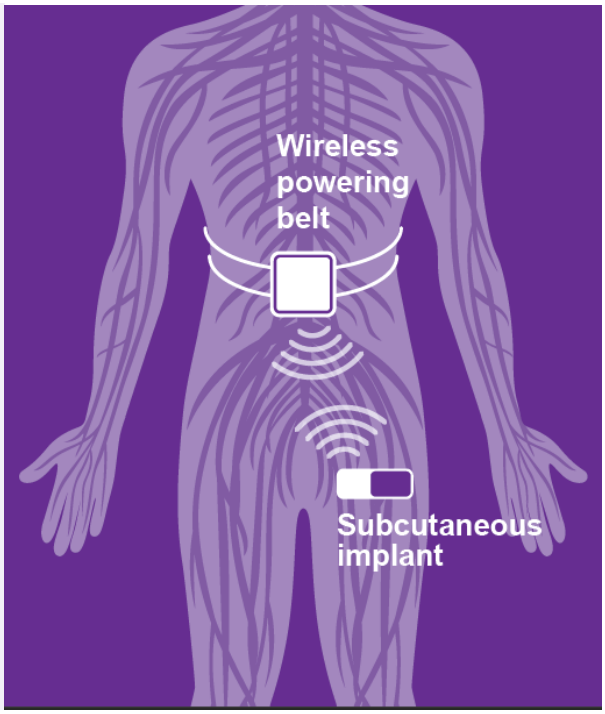
Specific objectives of Optogenerapy were demonstrating a miniaturized implant, developing stable therapeutic cell lines, develop industrial micro-injection molding processes for

manufacturing the minimally invasive implant and prove biocompatibility and therapeutical efficiency of the implant by in vitro and in vivo testing.

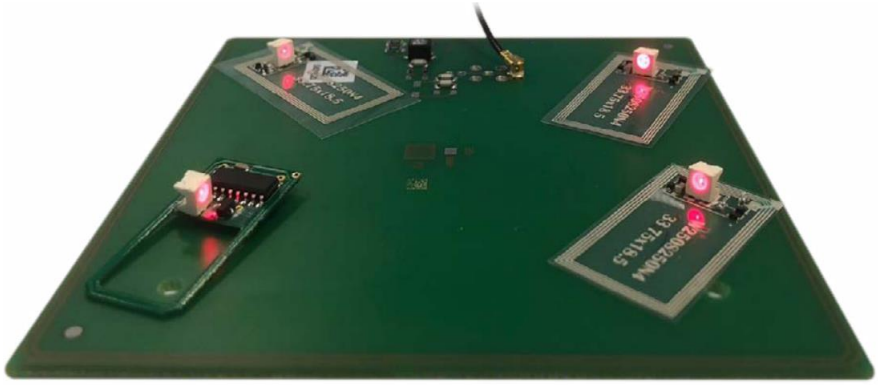
Figure 2 The Optogenerapy implantable device



a. Mock-up



b. External controller



c. The optoelectronics module.

a) The mock-up shows the two components of the implant; the optoelectronics module (see fig 2c) and the drug delivery cell chamber which encapsulates the cells, b) the external controller of the implant, a wireless powering belt, activates the electronics in the implant, c) the optoelectronics module has an electromagnetic antenna to activate the electronics in the device by the wireless powering belt using electromagnetic energy, and an optoelectronic unit which controls the beta-interferon (INFβ) generated.

Source figure a and b: The Optogenerapy consortium (28).
Source figure c: Mashayekhi et al. (2018) (29).

To date (early 2021) the implant is still in the early preclinical development stage. Preclinical trials such as evaluating the biocompatibility and the therapeutic efficacy of the implant in mice have been performed (30). However, no first-in-man clinical testing has yet taken place, and therefore no safety or efficacy data has been collected.

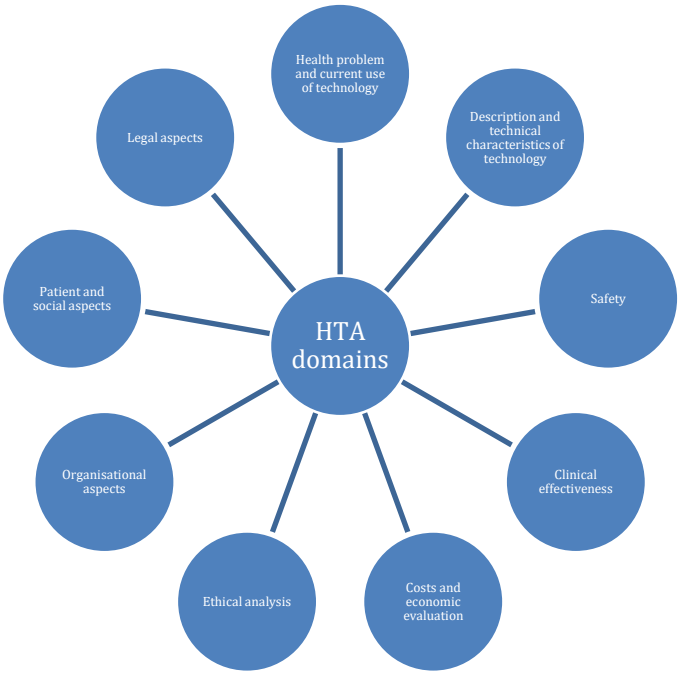
(EARLY) HEALTH TECHNOLOGY ASSESSMENT

To examine the potential health economic impact of a new medical device it is essential to do a full-body check of the new technology. This can be done by performing a health technology assessment (HTA). The fundamental reason behind an HTA is that money can only be spent once, which means you have to invest it wisely. There are various moments in time in which an HTA can be performed: when justifying private and public research investments (so-called 'very early HTA'), at the beginning and during the development of the device (so-called 'early HTA'), or later on when the final product has been tested in clinical trials and is ready to be launched (so-called 'classical HTA'). IJzerman et al. (2017) defined early HTA as *"all methods used to inform industry and other stakeholders about the potential value of new medical products in development, including methods to quantify and manage uncertainty"* (31). The primary distinction between early and classical HTA is the more iterative process of early HTA. There is room to explore the potential health effects and outcomes, identify gaps of the technology, and the ability to still make important changes to the device (32). Whereas in classical HTA, policymakers and industry are informed on the payments and market clearance of the device based on clinical outcomes (32).

The European network for Health Technology Assessment (EUnetHTA) has developed a methodological HTA framework (the HTA Core Model) for the assessment of pharmaceuticals, medical and surgical interventions, diagnostic technologies and screening (33,34). The HTA Core Model reflects the multidisciplinary nature of HTA and contains nine domains that should all be assessed (Figure 3).

In short, the domain health problem and current use of technology examine the target population and current care (commonly known as the background information, see section *Multiple Sclerosis*). Description and technical characteristics of the technology describe the technology under investigation (see section *Cell-based optogenetics drug delivery implant)*. Safety issues of the new technology have to be examined, such as health safety issues or any potentially harmful effects to patients. Clinical effectiveness (the magnitude of health benefits for the patient) can be examined under ideal circumstances (for example, in randomized clinical trials) or using real-world data. The costs and economic evaluation domain informs value-for-money judgements (see section *Economic Evaluations*). The ethical analysis explores the social and moral norms related to the technology to recognize the consequences of the implementation of technology on society. Organizational aspects concern issues such as the health delivery process, the structure of the healthcare systems, managerial issues, and acceptance of the technology. Patient and social aspects refer to the patients' perspective and the perspective of social groups towards the new technology. Along with how the patients and social groups evaluate the technology and the potential impact of the technology to society (see section *Stakeholder preferences: the patients' perspective*). Finally, legal aspects concern rules and regulations regarding the implementation of new technology (33). The nine domains are intertwined with each other and the information gathered may be used in multiple domains (33,34).

Figure 3 The nine domains of the HTA Core Model



HTA: health technology assessment.

Medical device development (and where does early HTA fit in?)

To develop a medical device there should be a (clinical) need for the product, either a need from the patients' perspective or healthcare professionals. There are various stages in the product development process: 1) basic research (for example, a health impact assessment to determine the potential benefits of the product); 2) translational research (product development decisions: involve the relevant stakeholders and examine the economic benefits by performing an economic evaluation); 3) clinical research (decide on clinical trial strategies and perform phase I-III clinical trials); and 4) market access and pricing (market access strategies) (35). In theory, these stages happen in succession to one another, but in reality, it is an iterative process. Especially stage 2, since the device is then still in development and, based on early HTA, changes to the product are possible.

While all nine HTA domains are important to examine, this thesis dives into two domains: costs and (early) economic evaluation, and the patient and social aspects. This choice was made because these two domains are of most interest when taking the perspective of a product developer and given the preclinical phase of the implant development. IJzerman and colleagues identified five reasons for early health economic evaluations: research and development (R&D) decisions, preclinical market assessment, portfolio decisions, clinical trial design, and market access and pricing strategies. Such an evaluation informs the industry in a timely manner regarding their investment (31). There are multiple methods to elicit stakeholder preferences, and these should not be limited to early health economic modelling (31). All in all, the outcome of early HTA help medical device developers answer the following question: is it worthwhile to continue developing this product?

Economic evaluations

An economic evaluation is defined as *"the comparative analysis of alternative courses of action in terms of both their costs and consequences"* (36). There are four types of economic evaluation: a cost-effectiveness

analysis (CEA), a cost-utility analysis (CUA), a cost-benefit analysis (CBA), and a cost-minimization analysis (CMA). In all four cases, the cost measurement is in monetary units. However, the consequences differ. For a CEA, there is a single health effect common to both alternative courses of action and the measurement of that consequence is in natural units (for example, number of relapses observed). For a CUA, it is possible to observe single or multiple health effects that are not necessarily common to both alternative courses of action and the measurement of that consequence is in healthy years (measured as quality-adjusted life years: QALYs). The CBA too has single or multiple health effects which are not necessarily common to both alternative courses of action, and the measurement of that consequence is in monetary units. Finally, for the CMA the health effect of both alternative courses are equivalent, therefore only differences in costs are examined (36).

It is important to perform an early evaluation of a medical product before substantial investments are made and to help guide decisions regarding further product developments. To date, ATMPs are (still) examined using current HTA methodologies while knowing that challenges such as effectiveness and safety uncertainties may be present because of the novelty of the products (37). A framework to guide the development of early-CEAs for new medical tests has been presented by Buisman et al (2016). While medical tests differ from medical devices (and the Optogenerapy cATMP), we still found it appropriate to adopt the early-CEA framework because of the early nature of the assessment. The framework has multiple steps: 1) narrow down the scope (i.e. define the target population by using the Patient population, Intervention, Comparator, and Outcome (PICO) method); 2) explore available data on current treatment strategies (what is current care and are there existing models of the disease); 3) develop a conceptual model; 4) early cost-effectiveness analysis (scenario analysis, sensitivity analysis, and headroom analysis); and finally 5) recommendation for further development (the go/ no-go decision) (38).

A go/no-go decision is partly based on the cost-effectiveness of the device. This is usually expressed using the incremental cost-effectiveness ratio (ICER = ΔC / ΔE, where ΔC is the difference in costs per patient and ΔE the difference is effects per patient of the new intervention versus the comparator) (39). The ICER is compared to a certain threshold, either (an)other ICER(s) for similar interventions or a societal willingness to pay (WTP) threshold (39). An intervention is the dominant cost-effective strategy when it leads to lower costs and more health effects than the comparator. An intervention can be cost-effective when there are more health effects but with higher costs. Furthermore, an intervention can also be cost-effective when there are cost-savings but this comes at a price: (acceptable) health loss. A decision has to be made whether the health effects are worth the costs (39).

Previously conducted economic evaluations do not present conclusive results on regarding the cost-effectiveness of DMTs for MS. The evaluations use different input parameters for their model, such as the perspective taken and what costs to include. For example, when taking the societal perspective, the model should include all the health care costs that are borne by society. Or the choice is made to include the costs relevant to a certain stakeholder (third-party payer, patient, or government perspective) (40). For instance, in France taking the French healthcare system perspective led to DMF dominating INFβ 30ug treatment. In Germany, the ICER of INFβ vs no active treatment is either €133,770 or €140,728 depending on the perspective taken (societal vs third-party payer perspective). From the Spanish societal perspective, INFβ 30ug was not cost-effective compared to GA (€117,914/QALY). In Sweden, the societal perspective found that NTZ was dominant over standard treatment (a mix of INFs and GA), whereas in the United Kingdom from the National Health Service (NHS) perspective NTZ was cost-effective (ICER below the threshold of £30,000) compared to INFs and GA in a subgroup analysis of persons with severe disease, but not in the general population (41). In the USA similar discrepant results are found (41). As such, it is difficult to pin the go/no-go decision purely on economic consequences to society, the industry, or other stakeholders involved.

Stakeholder preferences: the patients' perspective

The go/no-go decision for further development of a medical device is also in part based on eliciting stakeholder preferences. Worldwide, HTA institutions recommend that there should be an (early) involvement of all the multiple stakeholders, such as the regulators, payers, manufacturers, patients (42), and the public (43). The rationale for involving the patient and public in HTA decisions is diverse. For example, patients and the public have a right to say how their taxes are used to finance publicly funded healthcare systems. Or, that involving the patient and public will make for more qualitative sound HTA decisions since their values and preferences will be included in the HTA. Thereby looking beyond clinical and cost-effectiveness and examining HTA from a broader perspective (43). Also, including the patients' perspective may increase the acceptability and adoption of HTA recommendations and the medical technologies examined because, inevitably, patients will be the ones using the medical products (43,44).

There are various methodologies available to involve the patient during HTA (45) and these can be incorporated into MS trials and clinical care. One approach is to include patient research partners. Thereby including persons with MS throughout the research process. They can provide expert knowledge on the disease, the use of the health technology in their daily lives, and assist in the dissemination of results (46). Another approach is to use patient-reported outcome measures (PROMs). For example, questionnaires on health-related quality of life (HRQOL) (47), or concerning disability, mood, or cognition (48). Furthermore, stated preferences methods such as discrete choice experiments (DCEs) can be used to value patients' experiences of a health technology beyond clinical outcome measures to examine what trade-offs a patient makes regarding the characteristics of health technology. In MS, DCEs primarily examine DMT-related trade-offs (49).

THESIS AIM

This thesis describes the early Health Technology Assessment of the Optogenerapy cell-based implantable device for patients with multiple sclerosis. The overall aim is to assess whether such a new mode of treatment administration can potentially be an addition to the current treatment landscape in MS care. To come to an overall conclusion, certain other questions must also be asked:

- What are the needs and preferences of relapsing-remitting multiple sclerosis patients when making their treatment decisions?
- What is the real-world health-related quality of life of persons with multiple sclerosis in Europe?
- What are the preferences for different modes of treatment administration of persons with multiple sclerosis?
- What is the potential cost-effectiveness of the Optogenerapy implant?

OUTLINE

This thesis consists of three parts. Part I explores the needs and health-related quality of life of persons with MS. In Part II we aim to quantity the needs of persons with MS using qualitative and quantitative measures. In Part III we assess the potential cost-effectiveness of the Optogenerapy cell-based implantable device for persons with MS.

Part I includes *Chapter 2* and *Chapter 3*. *Chapter 2* examines the needs and preferences of persons with RRMS when making treatment decisions. This was done by performing a systematic literature review. *Chapter 3* investigates the real-world HRQOL of persons with MS using both generic and disease-specific HRQOL instruments in several European countries (the Netherlands, France, the United Kingdom, Spain, Germany, and Italy), and compared the HRQOL among these countries. Data was gathered by performing a cross-sectional, observational online web-based survey.

Part II includes *Chapter 4 and Chapter 5*. In *Chapter 4* we wanted to understand the treatment decision-making process from the patient perspective and to explore the possible acceptance of an implant to treat MS. This was done by conducting focus group sessions in the Netherlands. *Chapter 5* quantifies patient preferences for three modes of treatment administration (implant, pills, injections) and assess which trade-offs persons with MS are willing to make regarding treatment characteristics. We used an online survey containing a discrete choice experiment to elicit patient preferences in three countries (the Netherlands, France, and the United Kingdom).

Part III includes *Chapter 6* in which we estimate the potential cost-effectiveness of the Optogenerapy implant compared to injectable INFβ treatment. This was done by performing a cost-effectiveness analysis.

Chapter 7 provides a general discussion, in which the main findings are presented, the implications of these results for stakeholders are assessed, lessons learnt, and future recommendations are given.

PART I

SETTING THE SCENE: WHAT ARE THE NEEDS OF MULTIPLE SCLEROSIS PATIENTS?

2

PATIENT NEEDS AND PREFERENCES IN RELAPSING-REMITTING MULTIPLE SCLEROSIS PATIENTS: A SYSTEMATIC REVIEW

L.A. Visser, C. Louapre, C.A. Uyl-de Groot, W.K. Redekop. Multiple Sclerosis and Related Disorders (2020).

ABSTRACT

Background: Considering the multiple treatments approved for multiple sclerosis (MS) by the Food and Drug Administration (FDA) and European Medicines Agency (EMA), determining a treatment strategy for patients with clinically isolated syndrome (CIS) and relapsing-remitting MS (RRMS) can be challenging. To date, an overview of the needs and preferences of patients at each treatment decision-making moment is lacking. Therefore, the aim of this systematic review is to examine the existing literature about the needs and preferences of patients with CIS and RRMS when making treatment decisions.

Methods: A systematic search was done using Embase, Medline, PsychINFO, Web of Science and Google Scholar. Eligibility criteria included whether the article described a study of adults with CIS/RRMS and reported patient needs or preferences regarding first-line disease modifying treatment (DMT) decisions. Publications were categorized by treatment decision: initiation of first DMT (D1), DMT adherence/discontinuation (D2a/D2b), and switch to a second DMT (D3). A separate category was created for stated preference studies such as discrete choice experiment methods to examine the relative importance of different treatment attributes. Publications were compared to identify key factors.

Results: The search yielded 2789 articles after removal of duplicates and 434 full-text publications were reviewed for eligibility. Twenty-four articles fulfilled all criteria: n=5 (D1), n=12 (D2a), n=13 (D2b), and n=3 (D3); six articles studied more than one treatment decision. The need for social support is important during D1. The most commonly reported reasons for adherence/discontinuation/switch included forgetfulness, side-effects, and injection-related reasons. Eight articles described preference studies; the most important DMT attributes were efficacy, mode and frequency of administration, and side-effect profile.

Conclusions: Understanding the needs and preferences of CIS/RRMS patients regarding DMT attributes and non-treatment related attributes are important to improve treatment decision-making and reduce non-adherence. Studies are needed to understand patient preferences upon treatment initiation. Furthermore, preference studies should include attributes based on the patient perspective.

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated, demyelinating disease of the CNS, affecting 2.3 million people worldwide (50,51). Patients with a clinically isolated syndrome (CIS) or relapsing-remitting MS (RRMS) are advised to start with a disease modifying treatment (DMT) as soon as possible in order to decrease the risk of subsequent relapses and to limit the risk of long-term disability (8,52).

The first-line DMTs currently available differ in their mode of action, mode of administration, risk profiles, monitoring requirements and side effects (9,51,52). Psychological issues such as accepting the diagnosis affect when and whether patients start a DMT (53). As such, it can be a challenge for both the patient and the clinician to determine the best treatment strategy. However, this array of choice may allow for a treatment strategy personalized to the needs of the individual patient. Therefore, insight into the patient needs and preferences regarding DMTs is important since this will help to guide both the patient and clinician in the treatment decisions for individual patients as well as general treatment selection policies.

The DMT practice guidelines by the American Academy of Neurology and the Association of British Neurologists both recommend that physicians consider patient preferences when starting and switching DMT (51,54). An overview of the needs and preferences of patients at each treatment decision-making moment is lacking. Decisions are ever changing depending on the clinical experiences, social events over time, treatment uncertainty, and whom to consult during the decision-making process. A recent critical interpretive synthesis by Eskyte et al. (2019) highlights the complexity of the treatment decision-making for patients with RRMS. Furthermore, a recently published systematic review evaluated the methodology used in MS patient preference studies (49). Therefore, we reviewed what has been published about the needs and preferences of patients with CIS or RRMS when making treatment decisions.

METHODS

Systematic literature search

The systematic literature search was conducted in November 2017, and updated in October 2019, using five databases (Embase, Medline, PsychINFO, Web of Science and Google Scholar) and database-specific search terms (Appendix A). After the search in 2017 was complete and prior to screening the articles on title and abstract, Cohen's Kappa (κ) was calculated. This was not repeated in 2019. The coefficient measures the degree of interrater reliability of the two reviewers (LV and KR), and is a method to establish the amount of agreement between the two reviewers taking into account that the agreement could be due to chance alone. Three categories of level of agreement were used: high (Kappa coefficient greater than 0.75), fair (Kappa coefficient between 0.40 and 0.75) and poor (Kappa coefficient less than 0.40) (55). Along with the interrater reliability test, the two reviewers reviewed all titles and abstracts independently, and any discrepancies were resolved by discussion. Full text were subsequently assessed, and studies were included in the review if all inclusion and exclusion criteria were met.

Inclusion and exclusion criteria

Articles were eligible for inclusion if they involved patients with CIS or RRMS, they reported patient needs or preferences regarding first-line DMT (including interferon beta (INF-β), glatiramer acetate (GA), dimethyl fumarate (DMF), and teriflunomide) decisions (i.e. decisions to start, adhere to, discontinue or switch DMT), patients were older than 18 years of age, quantitative or qualitative studies, and in the English language. No publication date restriction was applied. Articles were excluded if the subject matter did not include MS, only involved patients with primary progressive MS (PPMS) or secondary progressive MS (SPMS), or when it was not clear what MS

type was studied, did not contain patient needs and preferences, and the article focused on 2nd line DMT (such as fingolimod, natalizumab, and alemtuzumab). Furthermore, editorials, review articles, book chapters, poster presentations, abstracts for congresses were omitted.

Categorization of the articles and data extraction

The publications were categorized according to the treatment decision they studied. The categories used were: the decision to start a first-line DMT (decision moment 1, D1), the decision to be adherent to treatment (decision moment 2a, D2a), the decision to discontinue treatment (decision moment 2b, D2b), and the decision to switch DMT (decision moment 3, D3). However, one exception to this rule was applied, which was to put all stated preference studies in a separate category.

Stated preference studies do not necessarily include information about the treatment decision moment but are used to quantify patient preferences for certain treatment options and side effects (56,57), efficacy of treatment (58), new products with new attributes (58), and preferences that go beyond clinical outcomes (59). Preference studies can also be used to understand physician prescription decisions (60). These studies use methods such as discrete choice experiments (DCEs) and conjoint analysis (CA), which are increasingly being applied in the MS field (56,58,61). Both methods use hypothetical scenarios to elicit patient preferences (56). The patient repeatedly chooses the scenario with attributes of the DMT he/she prefers the most, thus capturing the strength of the preference (56,62,63). The terms DCE and CA have incorrectly been used interchangeably, thus while some stated preference studies have been described as "CA", strictly speaking they are DCEs. The main difference between DCEs and CAs are that DCEs are based on the theory of choice behaviour, whereas CA is based on a mathematical theory (64). Thus, when applicable, in this review, CA are referred to as DCEs.

For each article, data was extracted regarding study design, methodology and patient characteristics. A narrative synthesis was conducted due to the heterogeneity of the results. The review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (65).

Quality assessment

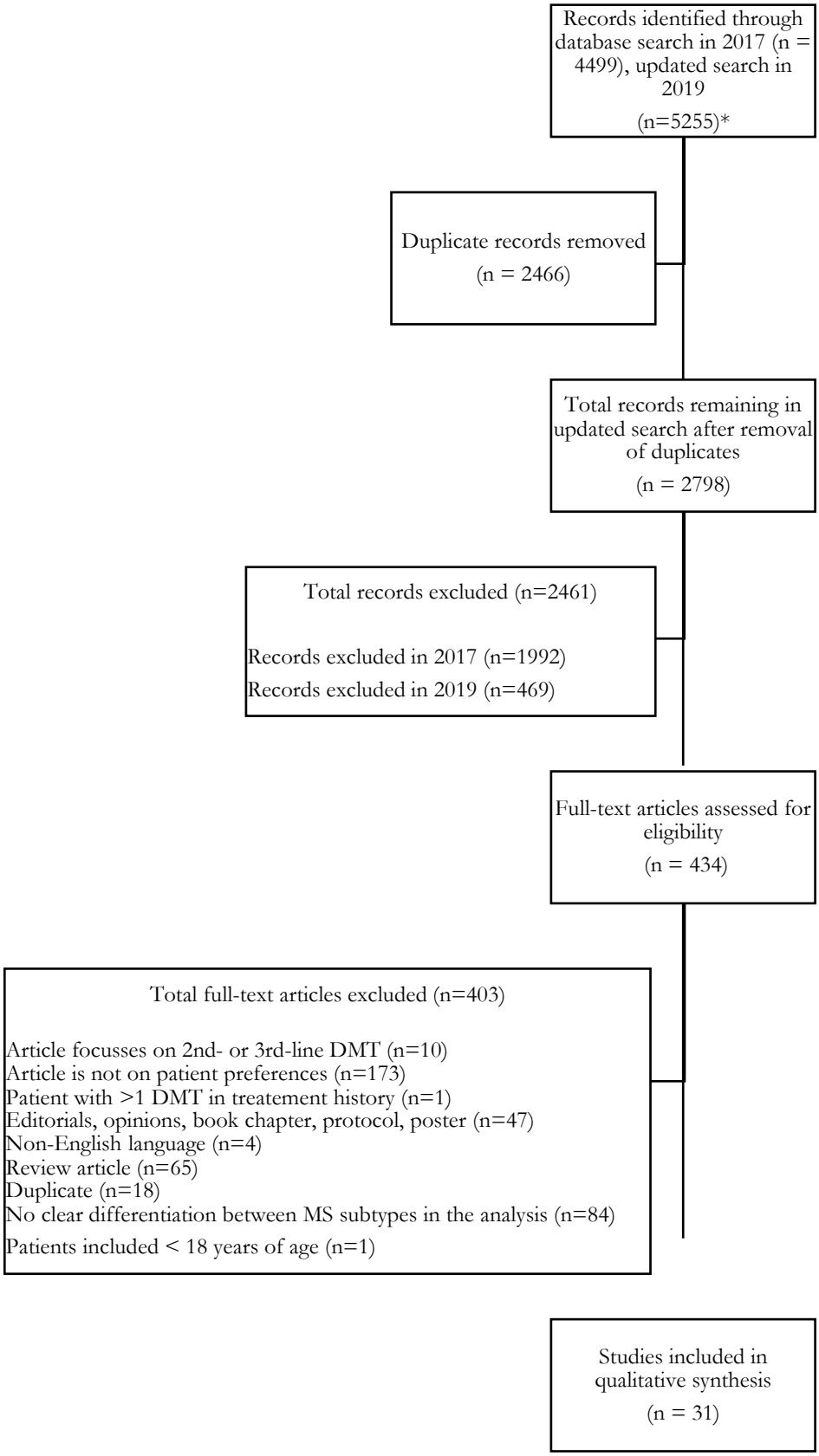
The quality of the studies were assessed based on whether the research question was clearly defined, the sampling methods used, the outcome measures and generalizability of the results.

RESULTS

Search outcomes

The updated search of databases yielded 5255 articles, of which 585 new were new references compared to the search in 2017 (see Figure 1). After removal of duplicates 2798 articles remained. A Cohen's Kappa coefficient of 0.62 was calculated, indicating a fair level of agreement between the reviewers about which articles were to be examined more carefully based on the full-text version. Consensus was improved via discussion amongst the reviewers. After screening titles and abstracts, 2461 articles were excluded, leaving 434 publications for full text review; however, if one of the reviewers felt that a full-text version was required, this was sufficient reason to retrieve the full-text version. Another 403 articles were excluded after full-text assessment, resulting in 31 articles for the review.

Figure 1 PRISMA statement flow diagram



*The search in November 2017 and October 2019 yielded 4499 and 5255 records, respectively, and identified 585 new references. The mismatch in the total number included can be attributed to database activities, such as updates of

records, the addition or removal of materials. The numbers in the diagram have been updated using backward correction (66).

Overview of included studies

Characteristics of the included studies are shown in Table 1. Five articles concerned D1 (67–71), twelve articles concerned D2a (67,68,80,72–79), thirteen concerned D2b (67,75,88–90,78,81–87), and three articles concerned D3 (69,71,83). Six articles covered more than one decision (67–69,71,75,78). Furthermore, seven articles examined patient preferences (91–97).

The majority of the papers were from the USA (n=8) (69,70,79,86,87,89,93,95), followed by Spain (n=4) (84,88,94,97), Italy (n=4) (78,80,82,90), The Netherlands (n=3) (68,71,96) and France (n=2) (67,83). Germany (91), Poland (72), Greece (73), Canada (81), Serbia (85), Lithuania (77) and the UK (92) all of which had one paper. Furthermore there were three multinational papers, two with European countries (75,76), and one paper with 22 international countries (74). Twenty-four studies used quantitative methods (67,72,81–90,73–80), four studies used qualitative methods (68–71) and seven used stated preference methods (91–97). One study included both CIS and RRMS patients (96), the remaining (n=30) had RRMS patients. A total of 13748 patient were included.

Table 1 Included study characteristics

Reference	Country	Study design	Sample size, n	Follow-up, months
Decision moment 1: treatment initiation (n=5)				
(67)	France	Cross-sectional observational survey	202	3
(68)	The Netherlands	Phenomenological research design	10	NA
(69)	USA	Phenomenological research design	20	NA
(70)	USA	Parallel-group randomized pilot study using content analysis	78	NA
(71)	The Netherlands	Phenomenological research design	25	NA
Decision moment 2a: treatment adherence (n=12)				
(74)	22 countries [a]	Multicentre observational phase IV study	2566	1
(75)	14 countries [b]	Multicentre prospective observational study	912	12
(76)	6 countries [c]	Multicentre prospective observational study	251	12
(79)	USA	Multicentre prospective observational study	708	2
(80)	Italy	Multicentre prospective observational study	285	12
(78)	Italy	Multicentre retrospective observational study	57	R: 5-34
(77)	Lithuania	Single centre observational study	207	3
(67)	France	Cross-sectional observational survey	202	3
(68)	The Netherlands	Phenomenological research design	10	NA
(71)	The Netherlands	Phenomenological research design	25	NA
(72)	Poland	Cross-sectional observational survey	226	NA
(73)	Greece	Multicentre prospective observational study	64	12
Decision moment 2b: treatment discontinuation (n=13)				
(75)	14 countries [b]	Multicentre prospective observational study	912	12
(86)	USA	Multicentre prospective study	234	3
(84)	Spain	Multicentre retrospective observational study	258	36
(78)	Italy	Multicentre retrospective open-label study	57	R: 5-34
(88)	Spain	Single centre retrospective observational study	155	Med: 34
(85)	Serbia	Single centre prospective cohort	290	72
(87)	USA	Single centre observational study	1471	M: 66
(67)	France	Cross-sectional observational survey	202	3
(89)	USA	Multicentre observational study	129	NA
(90)	Italy	Multicentre prospective observational study	520	M: 15
(72)	Canada	Single centre retrospective study	119	NA
(82)	Italy	Multicentre retrospective observational study	1832	12
(83)	France	Multicentre prospective observational study	881	60
Decision moment 3: treatment switch (n=3)				
(67)	France	Cross-sectional observational survey	202	3
(69)	USA	Phenomenological research design	20	NA
(71)	The Netherlands	Phenomenological research design	25	NA
Stated preference studies (n=7)				
(92)	UK	Discrete choice experiment	350	NA
(91)	Germany	Discrete choice experiment [e]	156	NA
(93)	USA	Discrete choice experiment [e]	289	NA
(94)	Spain	Ratings based conjoint analysis	221	NA
(95)	USA	Ratings based conjoint analysis	50	NA
(96) [d]	The Netherlands	Best-worst scaling	185	NA
(97)	Spain	Undefined ranking technique	37	NA

M: mean, Med: median, NA: not applicable, R: range, USA: United States of America, [a] Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, German, Iran, Ireland, Israel, Italy, Mexico, the Netherlands, Portugal, Spain, Sweden, Switzerland, the United Kingdom, Venezuela, [b] Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Lithuania, Portugal, Slovakia, Switzerland, The Netherlands, United Kingdom, [c] Finland, Greece, the Netherlands, Norway, Portugal, and Sweden, [d] Kremer et al. (2016) had a two-step approach regarding data collection, at first a nominal group technique was applied and those results were used as input for the best-worst scaling. [e] the authors described this as a "Choice-based conjoint analysis".

Decision moment 1: treatment initiation

A total of five studies concerned the decision to start a DMT. The patient characteristics of studies described in the different papers can be found in Table 2 section "Decision moment 1". Patient age ranged from 27-64 years old, an average of 75.5% were female and patients had a mean disease duration of 2-11 years. Most patients used an injectable DMT (n=228[68.1%]). One study included only patients not currently using a DMT (n=78[23.3%]) (70).

The study conducted in France by de Seze et al. (2012) is a quantitative study during which data were collected through physician and patient surveys. The four remaining studies are qualitative studies of which three used a phenomenological research design (68,69,71) and one used content analysis (70) to gather their data (Table 1). These types of studies analyse the meaning of the participants' own experiences through interviews. These experiences are then grouped into themes (98,99). The interviews by de Ceuninck van Capelle et al. (2017), Miller et al. (2006) and van Reenen et al. (2019) revealed four, seven, and three themes, respectively (Table 3). Schoor et al. (2019) analysed audio recordings of RRMS patients receiving their first motivational interviewing cognitive behaviour therapy to evaluate treatment (re-)initiation. The aim of all five studies differed.

De Seze et al. (2012) found that the patients' most important consideration when choosing a treatment was efficacy of the DMT (n=38 [42.2%]), followed by injection frequency (n=25[27.8%]), side effects (n=14[15.6%]) and mode of administration (specifically whether the patient would receive help with injections) (n=11[5.4%]). The patients in the qualitative studies did not indicate the most important factors that determined their treatment choice. Common factors such as efficacy (67,68,70), injection-related reasons (67–70), side effects (67,69,70) and mode of administration (67,69,70) were mentioned in both the quantitative and qualitative studies. Barriers to start taking a DMT were mentioned only by the patients interviewed by de Ceuninck van Capelle et al. (2017). Schoor et al. (2019) focused their analyses on reasons for not starting to take a DMT, furthermore they were the only study in which the patients mentioned costs being a factor in their treatment decision.

A common theme in the phenomenological studies was the importance of social support when choosing a DMT. These studies found that choosing a DMT is a social affair since patients discuss the treatment options with family, friends, and their healthcare providers (68,69,71). The views of family and friends were taken into consideration when deciding to choose (68,69,71) or not to choose a DMT (68). Another common theme was the feeling of having some form of control over their disease and lives when starting a DMT. This feeling of control can be obtained by controlling the disease progression (68,71) or controlling when, where and how to administer their treatment (69).

Table 2 Patient characteristics in the studies (categorized by decision moment, followed by stated preference studies)

Reference	Age, years	Female, %	Mean disease duration, years	Type of DMT (%)	Previous use of DMT	Duration of DMT treatment, years
Decision moment 1: treatment initiation						
(67)	M: 40.7	75.2	M: 8.0	im INFβ-1a (46) sc INFβ-1a (15.8) sc INFβ-1b (20.3) GA (17.8)	TE: DMT ≥ 3 months	M: 3.0
(68)	R: 27-51	80	M: < 2	INFβ-1a (30) GA (30) 2nd line DMT (10)- No treatment (30)	TN or TE	NR
(69)	R: 39-64	70	M: 9	GA (100)	TE	R: 1-7
(70)	M:45.6	88.5	11.4	No treatment (100)	TN or TE	NR
(71)	44	64	M: 7	Teriflunomide (40) Dimethyl Fumarate (60)	TE	NR
Decision moment 2a: treatment adherence						
(74)	M: 39.7	73.1	M: 6.0	im INFβ-1a (29.8) sc INFβ-1a 22μg (9.5) sc INFβ-1a 44μg (19.9) INFβ-1b (22.3) GA (18.5)	TE: DMT monotherapy ≥ 6 months	M: 2.58
(75)	M: 36.3	73.7	M: 2.8	sc INFβ-1a, RebiSmart (100)	TN or TE: ≤ 6weeks RebiSmart	NR
(76)	M: 35.8	66.1	M: 1.5	sc INFβ-1a (100)	TN or TE: ≤ 6 weeks sc INFβ-1a	NR
(77)	M: 42.9	68.6	M: 8.2	sc INFβ-1a (35.3) im INFβ-1a (17.9) sc INFβ-1b (19.3) GA (27.5)	TE: injectable DMT monotherapy	M: 5.0
(78)	M: 38.9	77.2	NR	INFβ-1a, RebiSmart (100)	TE: RebiSmart	NR
(79)	M: 43.4	76.7	M: 7.3	im INFβ-1a (28) sc INFβ-1a (19) INFβ-1b (25) GA (28)	TE: monotherapy injectable DMT ≥ 6 months	NR
(67)	M: 40.7	75.2	M: 8.0	im INFβ-1a (46) sc INFβ-1a (15.8) sc INFβ-1b (20.3) GA (17.8)	TE: DMT ≥ 3 months	M: 3.0

				im INFβ-1a (NR) sc INFβ-1a (NR) sc INFβ-1b (NR)		
(80)	M: 36.1	69.5	NR	GA (NR)	TN	NR
				INFβ-1a (30) GA (30) 2nd line DMT (10)[d]		
(68)	R: 27-51	80	M: < 2	No treatment (30)	TN or TE	NR
				Teriflunomide (40)		
(71)	44	64	M: 7	Dimethyl Fumarate (60)	TE	NR
				im INFβ-1a (19.0) sc INFβ-1a (13.2) sc INFβ-1b (29.6) sc INFβ-1b (12.8) GA (12.3)		
(72)	M: 37.3	73.4	NR [b]	Dimethyl Fumarate (12.8)	TE: DMT ≥ 6 months	NR
(73)	M: 64	78.1	M: 2.1	INFβ-1a, RebiSmart (100)	TE: ≤ 6weeks RebiSmart	1
Decision moment 2b: treatment discontinuation						
(84)	M: 40.7	67.8	M: 8.9	INFβ-1a, RebiSmart (100)	TE: RebiSmart	NR
(75)	M: 36.3	73.7	M:2.8	sc INFβ-1a, RebiSmart (100)	TN or TE: ≤ 6weeks RebiSmart	NR
				INFβ-1a (58.27)		INFβ-1a: 3.7
(85)	M: 38.0	71.4	M: 10.7	INFβ-1b (41.72)	TN	INFβ-1b: 3.2
(78)	M: 38.9	77.2	NR	INFβ-1a, RebiSmart (100)	TE: RebiSmart	NR
(86)	NR [c]	NR [c]	NR [c]	NR [c]	TN or TE with INFβ	NR
				im INFβ-1a (46) sc INFβ-1a (15.8) sc INFβ-1b (20.3)		
(67)	M: 40.7	75.2	M: 8.0	GA (17.8)	TE: DMT ≥ 3 months	M: 3.0
				sc INFβ-1a (27.9) im INFβ-1a (2.3) INFβ-1b (8.2)		
(87)	M: 38.4	75.3	M: 6.0	GA (61.6)	TE: injectable DMT	M: 8.6
(88)	M: 37	68.3	NR	GA (100)	TN or TE with INFβ	NR
				im INFβ-1a (Avonex) (43) sc INFβ-1a (Rebif) (26.5) sc INFβ-1b (Betaseron) (29.1) GA (70.9) DF (1.3)		
(89)	M: 44.6	83.7	NR	Novantrone (1.3)	TE	NR

				2nd line DMT (28) [d, f] (10)		
(90)	M: 43	70	NR	INFβ-1a/-1b/pegylated INF (22.3) DF (38.7) Teriflunomide (11.5) GA (27.5)	TN or TE (70%)	NR
(81)	M: 42.6	75	R: 6.3-12	Teriflunomide (100)	TN or TE (76%)	M; 14
(82)	M: 40	70.3	M: 9.1	im INFβ-1a (5.6) sc INFβ-1a (3.9) INFβ-1b (8.9) GA (9.4) Dimethyl fumarate (57.1) Teriflunomide (15.1)	TN or TE (65.8%)	NR
(83)	39.9	75.8	M: 8.1	GA (100)	TN or TE (58.2%)	NR
Decision moment 3: treatment switch						
(67)	M: 40.7	75.2	M: 8.0	im INFβ-1a (46) sc INFβ-1a (15.8) sc INFβ-1b (20.3) GA (17.8)	TE: DMT ≥ 3 months	M: 3.0
(69)	R: 39-64	70	M: 9	GA (100)	TE	R: 1-7
(71)	44	64	M: 7	Teriflunomide (40) Dimethyl Fumarate (60)	TE	NR
Stated preference studies						
(92)	M: 38.6	81	M: 5.2 [a]	im INFβ-1a (9) sc INFβ-1a (2) sc INFβ-1a (5) sc INFβ-1b (3) sc INFβ-1b (4) GA (11) Teriflunomide (2) Dimethyl fumarate (35) 2nd line DMT (28) [d, e, f]	TE	NR
(91)	M: 37	68.6	M: 4.8 [a]	Treatment naïve (15.4) Experience with parenteral DMT (58.9) Experience with oral and parenteral DMT (25.6)	TN or TE	NR

(93)	M: 42.0	76.4	M: 8.1 [a]	No DMT (17.4) Interferons (22.5) GA (22.9) 2nd line DMT (31.8) [d, f, g] Other (2.4)	TN or TE	NR
(94)	M: 42.1	68.3	M: 9.1	First-line injectable (43.9) Dimethyl fumarate (15.4) 2nd line DMT (31.2) [d, f]	TE	NR
(95)	M: 42.7	74	5.1 [a]	No current treatment (18) Interferon beta (26) GA (34) 2nd line DMT (22) [d, f, g]	TE	NR
(96)	M: 42.1	82.7	M: 6.4	Treatment naïve (14.6) Currently taking DMT (70.8)	TN or TE	NR
(97)	M: 38.6	78.4	M: 8.5 [a] *	Injectable agents (43.2) Dimethyl fumarate (24.3) 2nd line DMT (16.2) [f]	TE	NR

DMT: disease modifying treatment, GA: glatiramer acetate, im: intramuscular, INFβ: beta interferon, M: mean, NR: not reported, R: range, sc: subcutaneous, TE: treatment experienced, TN: treatment naïve, [a] time since diagnosis, [b] reported in categories (<1 year, 1-5 years, 6-10 years, > 10years disease duration) where 28.3% of the patients had a disease duration > 10 years, [c] supplemental data has to be requested, [d] Fingolimod, [e] Alemtuzumab, [f] Natalizumab, [g] Rituximab.

Table 3 Study aim and reasons for treatment initiation (D1).

Reference	Aim		
		Treatment choice	**Treatment considerations**
(67)	To describe the perceived benefits and limitations of current DMT for MS, treatment adherence, impact on quality of life and daily living, and treatment expectations and needs	Followed advice of neurologist (n=112, 55.4%) DMT proposed by neurologist, patient involved in DMT decision-making process (n=81, 40.1%) Patient requested DMT (n=9, 4.5%)	Efficacy (n=38, 42.2%) Injection frequency (n=25, 27.8%) Anticipated side effects (n=14, 15.6%) Whether they could get help with their injections (n=11, 5.4%)
(70)	To investigate avoidance coping and treatment adherence	**Reasons not to take a DMT**	
		Mild disease course (n=5)	No need due to few symptoms of MS No relapses in the past 5 years Monitor disease progression by regularly seeing the neurologist and obtaining MRIs
		Costs (n=11)	Unable to afford a DMT/ MRI/ consultation with the neurologist Would use a DMT if it were affordable to them
		Side effects (n=19) [b]	Severe side effects Injection-related reasons Needle phobia Would use a DMT if there were no side effects
		Avoidance coping [c]	Choose not to monitor their disease Sceptical about the level of efficacy Do not trust the physician or pharmaceutical company Doubting diagnosis / minimizing MS symptoms Irrational thoughts about pros or cons of taking DMT Acknowledge avoidance
(68)	To explore patients' perspective on using DMTs [a]	**Themes**	**Considerations within the themes**
		Importance of social support (n=5)	Discuss DMT choice with family, friends and healthcare providers
		Managing inevitable decline (n=4)	Proactive in managing and controlling care Taking control over the disease Level of efficacy

		Constant confrontation with the disease (n=6)	Injection-related reasons Mode of administration Barriers (ex: future pregnancy, concerns with travelling)
		Hope of delaying the progression of the disease (n=3)	*Related to treatment adherence (see table 4)*
(69)	To examine the experience of MS patients with GA	Choosing GA	Side effect profile Discuss DMT choice with family, friends and healthcare providers Choosing a DMT is a complex process
		Self-managing care	Proactive in managing and controlling care Patients requested GA Taking control over the disease
		Injecting	Injection-related reasons
		Healthy lifestyle	Taking control over the disease
		Side effects	Side effect profile
		Support	The importance of family and healthcare provider support
		Advice to others	Help others with their disease
(71)	To understand what is means for people with RRMS to live with a chronic illness and use oral medication	Trying to hold on to one's familiar life	Feeling overwhelmed by insecurities Feeling obliged to do something Postponing the constant confrontation with being sick Experiencing support and reinforcement Doing what fits bets personally
		Becoming familiar with one's new life	*Related to treatment adherence (see table 4)*
		Being familiar with one's new life	NA

DMT: disease modifying treatments, GA: glatiramer acetate, im: intramuscular, INFβ: beta interferon, MS: multiple sclerosis, NA: not applicable, theme is not related to the three treatment decision moments, sc: subcutaneous, [a] Each theme mentions how many patients spoke of this theme, though this does not indicate a higher preferences for one theme over another theme, [b] Patients within this theme had past experience with a treatment, [c] Avoidance coping was characterized by patients that avoid engaging in care and rationalized their decision not to take a treatment.

Decision moment 2a: treatment adherence

A total of twelve studies examined treatment adherence. The characteristics of the patients in these studies can be found in Table 2 section "Decision moment 2a". Patient age ranged from 27-51 years old, an average of 79.6 % were female and patients had a mean disease duration of 1.5-8.2 years. Three studies examined adherence of auto-injectors (n=1033[18.7%]) (73,75,78), one examined oral DMTs (n=25[0.45%]) (71), while the other studies examined adherence of conventional injectables (n=4422[80.2%]). One study also included patients who were on a 2nd-line treatment or currently not on treatment (68).

Data was collected through patient questionnaires (n=8) (67,72,74,75,77–80), diary entry by patients reporting reasons for missed injections (n=2) (73,76) and patient interviews (n=2) (68,71) (Table 1). The aims of the studies were somewhat similar since all assessed treatment adherence (Appendix B). The definition of adherence was dissimilar across the studies. The percentage of patients not missing a single injection ranged from 63-75%.

The quantitative studies did not discuss reasons for adherence (67,72–79). The most commonly reported reasons for non-adherence (i.e. missing a single injection) were forgetting to administer treatment (n=10[8.7-58%]), injection-related reasons (n=8[3-28%]), and common side effects of DMT (n=10[3.7-25.5%]) (Table 4). Patients in the qualitative studies mentioned that they hoped that adhering to the treatment would delay disease progression, that they are more motivated to adhere to treatment when they 'feel good' (68) and that they feel a responsibility to adhere to maximize efficacy (71). Other than sometimes forgetting the DMT, the patients in the qualitative studies did not mention reasons for non-adherence (68,71).

Decision moment 2b: treatment discontinuation

A total of thirteen studies examined treatment discontinuation. The patient characteristics can be found in Table 2, section "Decision moment 2b". Patients age ranged from 36.3-44.6 years old, an average of 73.7% were female and had a mean disease duration of 6-12 years. Three studies examined discontinuation rates of an auto-injector (n=1227[17.3%]) (75,78,84), one study examined only oral DMTs (n=119[1.68%]) (81). The remaining examined discontinuation of conventional injectables and oral DMTs.

All included studies were observational studies. The aim of the studies differed somewhat, though all evaluating adherence, persistence or reasons for discontinuing treatment (Appendix B). The definition of adherence was dissimilar across the studies, though the definition of persistence was uniform. The percentage of patients' discontinuing treatment ranged from 12.8-50.0%.

The most commonly reported reason for discontinuation with DMT treatment was the occurrence of adverse events (n=12[6-48%]), followed by the voluntary decision by the patient (n=7[4-38%]), and perceived lack of efficacy (n=6[2-34%]) (Table 5). Elaborations on what the reasons were for the voluntary discontinuation were not given.

Table 4 Reasons for treatment (non)adherence (D2a)

Reference	Reasons for adherence	Reasons for non-adherence														
		Treatment related						Not treatment related								
		Common side effects of DMT	Injection-related reasons	Dosage inconvenience	Perceived lack of efficacy	Forgot to administer	Other	MS related symptoms	Headache	Miscellaneous	Costs	(Planning a) Pregnancy	Travel	Neurologists' advice	Surgery	Coping
(74)	NR	9-13%[1,2]	3-20%[3-7]	10%	2%	50%	17%	6- 15%[10-12]	10%	5%[14]	2%	1%				
(75)	NR	4%[1]	3-19%[4-6]			37%	23%	10%[13]								
(76)	NR	11%[1]	2-19%[4-6]			51%	19%	6%								
(77)	NR	26%				26%							33%			
(78)	NR	X[1,2]	X[4]			9%	X[9]	X[10]								
(79)	NR	5%	3-22%[4,5]	8%	3%	58%	22%	2-12%[10-12]	1%	4%	4%	0%				
(67) [a]	NR	14%[1,2]	28%[8]			39%						3%	8-22%[15, 16]	11%	2%	9%[17]
(80)	NR	4-7%[1,2]	1-13%[3,4,5,6,7]	1%	4%	17%	7%	4-8%[10-12]	4%	1%[14]		1%				
(72) [b]	NR	17%	11-19[3,5,7]			18%	13-19[18,19,20,21]	13[12]		13%[14]			23%			
(73)	NR	16%[1]				19%	19%						11%			

DMT: disease modifying treatment, NR: not reported, X: reason given in the article though no percentages given. [a] Uncertainty about the results because the same reasons and percentages given for skipping an injection (non-adherence) as well as stopping treatment (discontinuation), [b] Percentages shown are based on the answer possibilities from the Multiple Sclerosis Treatment Adherence Questionnaire of those patients whom find these barriers "moderately important" (for the reason 'nobody to administer') to "extremely important" (all other reasons), [1]Flu-like symptoms, [2] skin reactions, [3] tired of taking injections, [4] pain at injection site, [5] injection anxiety, [6] did not feel the need for every injection, [7] nobody able to administer, [8] weariness with injections, [9] other medical reasons, [10] fatigue, [11] weakness, [12] depression, [13] tired, [14] did not pick up medicine, [15] travel, [16] holidays, [17] to help not thinking about being ill, [18] dissatisfied with the treatment, [19] do not want taking treatment to interfere with activities/ responsibilities, [20] did not feel like taking the treatment, [21] too busy.

Table 5 Reasons for discontinuation (D2b)

Reference	Reasons for discontinuation														
	Treatment related							Not treatment related							
	Occurrence of adverse events	Serious adverse events	Treatment failure	Injection-related reasons	Treatment change	Perceived lack of efficacy	Voluntary decision	Non-adherence to treatment	Cancer	Lost to follow-up	Other	Insurance problems	Unknown	Costs	(Planning a) Pregnancy
(84)	13%					11%	8%	6%							
(75)	6%				3%	2%									
(85)	17%		54%				4%				4%				21%
(79)	33%					11%	22%		11%						22%
(86)	22%						38%			19%	16%	6%			
(67) [a]	14%			28%[3]							2-39%[4-9]				3%
(87)	48%[1]	18%[2]		18%		34%	8%				8%[10]		9%	3%	
(88)		2%		13%		17%									
(89) [b]	67%			51%							55%[11]				
(90)	56%		37%			6% [c]	2%								
(81)	42%[12]		32%				26%								
(82)	17-44%[d,1]		25%								3%				
(83)	15-23%[1]	2%				39%					1-21%[10,13,14]				1%

[a] Uncertainty about the results because the same reasons and percentages given for skipping an injection (non-adherence) as well as stopping treatment (discontinuation), [b] Percentages shown are based on the answer possibilities from the Multiple Sclerosis Treatment Adherence Questionnaire, however unknown how the patients responded on the

four-point scale “not at all important” to “extremely important”, and not all barriers of the scale were presented, [c] Combined tolerability and efficacy issues, [d] range of adverse events such as lymphopenia, skin rash, liver enzyme increase, [1] intolerability, [2] high levels of neutralizing antibodies, [3] weariness with the injections, [4] travel, [5] holidays, [6] neurologists' advice to stop, [7] surgery, [8] coping, [9] forgot to administer, [10] unrelated medical problems or personal issues, [11] dissatisfaction with treatment, [12] gastrointestinal side effects, [13] abnormal laboratory tests, [14] planned discontinuation.

Decision moment 3: switching treatment

Three studies included data on reasons why patients switch DMT. The patient characteristics can be found in Table 2 section "Decision moment 3". Patients age ranged from 29-64 years old, an average of 69.7% were female and had a mean disease duration of 7-9 years. The majority of the patients used an injectable DMT (n=222[89.9%]), and the other patients used oral treatment (n=25[10.1%]). Study design can be found in the text under Decision moment 1.

There were four common reasons why patients switched treatment: the switch was initiated by the healthcare provider, poor tolerability, occurrence of adverse events and requested by the patient. Details on why the switch was initiated by the healthcare provider was not given (67,68). Patients switched from injectables to oral treatment because orals were newly available to them, intolerance and increased disease activity (71).

Preference studies

A total of seven stated preference studies were included. The patient demographics can be found in Table 2. An average of 184 patients participated in a preference study, ranging from 37-350 inclusions, with a mean age ranging from 38.6-43 years, an average of 75.6% were female, and a mean disease duration ranging from 5.1-9.1 years. Four studies examined the preferences of patients with treatment experience (TE) (92,94,95,97), and the remaining three studied a combination of TN and TE patents (91,93,96).

Three of the studies (42.8%) used a DCE to determine the preferences of the patients (91–93). Other methods included a ratings-based CA (n=2 [28.5%]) (94,95), the best-worst scaling method (BWS) (n=1[14.3%) (96), and an undefined ranking technique (n=1[14.3%]) (97) (Table 1).

For the ratings-based CA the patients had to rank the attributes from most to least preferred using a card-sorting technique (94,95). When adopting the BWS method the patient has to compare the different attributes offered and indicate what attributes he/she prefers the most compared to what he/she prefers the least (62). This task is repeated for various best-worse scenarios (62). There are three types of BWS (100). Kremer et al. (2016) used the "BWS object case", which does not include levels within an attribute. The results from the study using the undefined ranking technique used a multidimensional unfolding approach to present preferences along a dimensional plane, allowing for visual interpretation of the preferences (97).

All of the included studies discussed patient preferences for different attributes of DMTs. The aim of the studies differed somewhat; such as the preference for oral versus injectable treatment (91), to study how patients trade-off the risks and benefits of DMTs (93,95), and general preferences of DMT attributes (92,94,96,97). Various methods were used to identify attributes, such as a literature review (91,92,94–97), using current clinical literature (93), consultation with clinical experts (91,93–97), DMT trials (93), and interviews (92) or focus groups (96) with patients. Wilson et al. (2014) conducted a pilot study to evaluate attributes and levels before the final DCE was distributed amongst patients; this pilot study helped to reduce the number of attributes, eliminating those that had no significant impact on patient preferences (93). Multiple elicitation formats were used to determine preferences, including a choice-based question format (91–93), ranking (97), rating (94,95) and a best-worse scale (96).

Attributes and levels

Whereas Webb et al. (2018) categorized 13 DMT attributes, we identified a range of 3-27 attributes and these have been clustered based on common characteristics (Table 6). The efficacy of the DMT was separated into two attributes ('preventing relapses' and 'delaying disease progression') and were included in six studies (92–97). Administration of the DMT was included in all studies (n=7), although three studies combined 'mode of administration' and 'frequency of administration' into one attribute (92,93,95), while the others defined them as separate entities. The side effects were

separated into three attributes. One study included two attributes on the risk of severe side effects (92) and one study looked at common side effects (91). Two studies separated the severity of the side effects into two attributes (93,95). Two studies included the side effects as an attribute, though did not specify the severity (96,97). Other attributes such as monitoring (92,96), safety (92,96), and symptom improvement (93,95,96) were also examined. None of the studies showed the same pattern when ranking the three most important attributes (Table 7). Generally the efficacy, administration and side-effect profile of the DMT were important.

The number of levels per attribute used in the studies ranged from 1 to 5 and not all levels were defined in the same manner (Table 6). Four studies had multiple levels for 'preventing relapses' (92–95). Bottomley et al. (2017) used percentages (either 60%, 70%, or 80%) to express how many patients would be relapse free after taking a DMT. Whereas other studies framed the attribute 'preventing relapses' as patients with MS having one relapse every one (93,95), two (93–95), three (95) or five (93–95) years using a DMT.

The results of the studies show that patients prefer a DMT that decreases relapse rate (93,94) and increases the percentage of patients being relapse free (92). One study, however, found that the 'preventing relapses' levels had no significant impact on preference (95). All five studies using multiple 'mode of administration' levels found that patients prefer oral DMTs over injection or infusion therapy (91–95). Four studies found that a higher risk of severe side effects was associated with a reduced preference (92–95). Both studies done by Wilson et al. (2014, 2015) revealed that minor side effects had no significant impact on patient preferences.

Subgroup analysis was done in five studies (91,92,94–96). Subgroup analysis examined whether demographic and clinical characteristics or treatment experience influenced preferences. Across the studies none of the same characteristics were analysed. One study found no significant differences in preference amongst the different subgroups (age, sex, time since diagnosis and severity of disease) (92). Utz et al. (2014) found that a higher expanded disability status scale (EDSS) score to be predictive for the preference of a pill over injectables. Wilson et al. (2015) found that patients older than 40 years of age preferred a DMT that prevents disease progression and are less averse to fatal risks than younger patients. One study found that males are more concerned about the influence of treatment on life style and life expectancy than females (96).

Three studies looked at the influence of time since diagnosis on preferences (92,94,96). One found that recently diagnosed patients (<1 year) place high importance on side effect risk compared to those with a longer disease duration (94). Another study found that patients with a longer disease duration were more concerned about the safety of the DMT (96). While Bottomley et al. (2017) did not observe a significant association between duration and preferences.

Three studies examined differences in treatment preferences for patients with and without treatment experience (94–96). One study found that treatment naïve patients and patients not using treatment at the time of survey administration (though had prior DMT experience) preferred a treatment with lower duration, type and severity of side effects than patients with treatment experience (96). Patients with previous DMT use preferred a treatment with high efficacy (94,96). One study found that patients using first-line DMT are more averse to fatal risks than those taking a second-line DMT (95). Furthermore, one study found that patients using oral medication value mode of administration more highly than those using injectables (96).

Quality of the studies

The studies were judged to be of sufficient quality and therefore no study was excluded.

Table 6 The DMT attributes included in the stated preference studies

Reference	Number of attributes (levels)	Attributes																							
		Efficacy		Administration		Side effects			Others																
		Preventing relapses	Delay progression	Mode of administration	Frequency of administration	Side effects	Severe side effects	Common side effects	Monitoring	Safety	Symptom improvement	MRI activity	Costs	Quality of life	Daily living	Uncertain future	Multi-drug interactions	DMT use by other MS patients	Travel	Pharmacotherapy	Development of DMT	Contact person at pharma company
(92)	7 (3-5)	X	X	X			X[15,16]		X	X													
(91)	3 (2-4)			X	X			X															
(93)	6 (3-4)	X	X	X			X	X			X												
(94)	5 (2-4)	X	X	X	X		X [a]																
(95)	8 (4)	X	X	X			X	X			X	X										X	
(96)	27 (1)	X[1,2]	X[3,4]	X	X[5,6]	X[7-9]			X	X	X	X	X[10,11]	X	X	X	X	X	X	X[12-14]	X	X
(97)	5 (1)	X	X	X	X	X[7]																	

NA: not applicable. [a] Trade-off between severity and frequency of the side effects, [1] Effect on relapse rate, [2] effect on the severity of relapse, [3] effect on disease progression, [4] effect on life expectancy, [5] frequency of administration, [6] duration of administration, [7] severity of side effects (not specified by the authors), [8] type of side effects (not specified by the authors), [9] duration of side effects, [10] insurance coverage, [11] total DMT costs, [12] pace of effect, [13] mode of action of DMT, [14] composition of DMT, [15] Risk of serious infection, [16] risk of serious fatigue.

Table 7 The DMT attributes ranked according to importance

Reference	**Attributes**																							
	Efficacy		Administration		Side effects			Others																
	Prevention relapse	Delay progression	Mode of administration	Frequency of administration	Side effects	Severe side effects	Common side effects	Monitoring	Safety	Symptom improvement	MRI activity	Costs	Quality of life	Daily living	Uncertain future	Multi-drug interactions	DMT use other MS patients	Travel	Pharmacotherapy	Development of DMT	Social support
(92)	2	3	1			5,6		7	4												
(91)			2	1			3														
(93)	5	3	4			1	6			2											
(94)	5	4	2	3			1														
(95)	7	6	2			1	4			3	5									8	
(96)	3[1], 5[2]	1[3], 11[4]	17	21[5],25[6]	4[7],10[8],13[9]			22	8	6	7	15[10], 20[11]	2	9	12	16	23	24	14[12], 18[13], 26[14]	19	27
(97)	2	1	4	5	3[7]																

Per study the most to least important attribute to least important is displayed (1: most – 27: least), the top three most important attributes have an underscore. [1] Effect on relapse rate, [2] effect on the severity of relapse, [3] effect on disease progression, [4] effect on life expectancy, [5] frequency of administration, [6] duration of administration, [7] severity of side effects (not specified by the authors), [8] type of side effects (not specified by the authors), [9] duration of side effects, [10] insurance coverage, [11] total DMT costs, [12] pace of effect, [13] mode of action of DMT, [14] composition of DMT.

DISCUSSION

This study was conducted to review what has been published about the needs and preferences of patients with CIS or RRMS when making treatment decisions. The 31 articles included were categorized according to the decision moment and patient preferences. The majority of the articles focused on treatment (non)adherence and discontinuation, while only a handful of the studies examined reasons why patients initiate or switch treatment. The most important treatment characteristics that influence DMT decision-making are the efficacy, mode of administration and side effect profile of the DMT. The stated preference studies revealed that treatments that reduce the risk of relapse, are orally administered and have minor side effects are preferred by patients.

We identified a gap in the literature since only five articles looked at treatment initiation amongst patients with RRMS and none of them included CIS. A plausible reason that no CIS patients were included could be due to the updated diagnostic criteria that allows for a patient with CIS to be diagnosed with clinically definite MS (CDMS) based on a single MRI (4). It has been estimated that patients with CIS have a 42-82% risk of developing CDMS without treatment (101). A meta-analysis of the short- and long-term clinical outcomes of CIS for patients with a high risk of CDMS showed that early use of IFN-β or GA therapy delayed the time to CDMS (102). The difficulty for patients with CIS or RRMS with a single relapse in deciding whether or not to start DMT is imaginable; while they may benefit from DMT use, they will also have to consider the possibility of never experiencing subsequent clinical consequences of MS. In order to understand whether a patient with CIS or early RRMS will consider starting treatment and what treatment aspects they deem important, a stated preference study could be held amongst early MS patients.

The primary reason given for non-adherence was forgetting to administer the treatment. Forgetfulness may be a result of cognitive decline (103) or treatment fatigue (104). Since non-adherence reduces a drug's efficacy, physicians should educate their patients on the importance of treatment adherence (54). However, the industry and patient organizations may also play a role in improving adherence and reducing forgetfulness. The development of MS-related mobile/electronic health technologies (mHealth/eHealth) may be a potential solution to accommodate these needs (105). An example of this is the MSdialog, which is a web- and mobile-based application that has been shown to improve adherence and patient-physician communication (106). Applications could not only help to improve administration by tracking injection frequency and setting reminders, but could also be used to address MS-related symptoms such as fatigue or provide education, monitor disease progression and motivate patients in whatever way needed (105,107). However, it is possible that some patients will benefit from mHealth/eHealth applications while others will not. For example, patients that already use web-based or mobile devices to look up health-related information are more willing to accept innovative ways to communicate with their physician (108). Moreover, older patients might not use technology as readily as younger patients (108).

However, non-adherence may also be a perfectly rational choice as patients may weigh the costs and benefits of following the treatment (109). A study amongst HIV patients in Australia found that treatment decision making depends on how the patient values the attributes of a treatment. Furthermore, intentional non-adherence relies more on treatment characteristics rather than patient characteristics (110). Similar to our results they found that efficacy, mode of administration and side effect profile of the DMT influence the treatment decision-making process. Therefore, we have to keep in mind that non-adherence can be the result of a patient consciously chooses not to follow physicians recommendations (111).

Different studies have observed that treatment adherence is related to healthcare utilization and healthcare costs. For example, Gerber and colleagues (2017) found that adherent patients (the majority using injectable DMTs) were 50% less likely to be hospitalized for MS-related reasons than non-adherent patients. Furthermore, another study found that non-adherent patients had higher MS-related general practitioner (GP) and specialist medical costs than other patients (112).

Two US studies using administrative claims data found that adherent patients have significantly lower relapse rates at 12-month follow-up (113,114), lower hospitalization rates (113,114), and total non-drug medical costs (114) than non-adherent patients. Total annual costs (such as treatment costs and productivity loss) for patients with at least one relapse are higher than clinically stable patients (115). Patient management programs (116–118) or specialty pharmacy care programs (119) may prove to be beneficial by increasing adherence (116–118), reducing healthcare utilization and non-pharmacy MS-related costs (116) or total MS-related costs (118). Tackling non-adherence through the implementation of such programs could lead to cost-savings in the healthcare sector.

As noted previously by Webb et al. (2018), the methods of data collection for determining DMT attributes can be improved. While all studies claim to research patient preferences only Kremer et al. (2016) and Bottomley et al. (2017) consulted patients in combination with a literature review (96) and consultation with clinicians to determine the attributes (92). In addition to literature review and interviews with clinicians, attributes should also be based on qualitative research amongst patients to make sure that the correct attributes and attributes that patients find important are included. Moreover, to make sure that none are omitted in order to avoid omitted variable bias (120). Future stated preference studies should consult MS patients by organizing focus groups and conducting interviews to determine attributes. As such, a more comprehensive list of attributes can be developed. In turn, this can lead to a better understanding of patient preferences that go beyond clinical outcomes (e.g. non-drug related preferences), an area that has not yet been extensively researched.

Subgroup analyses in the preference studies showed that there was no single demographic, clinical or treatment characteristic that was dominant in determining preference. The primary reason is the studies examined different characteristics in different ways. Future studies should analyse the same subgroups to increase the comparability of results between studies. Once existing patterns in patient preferences have been found, they could be used to help patients and physicians to decide which treatment is most appropriate for a particular patient. Additionally, this could improve adherence since the treatment decision will have been based on personal preferences. For now, this heterogeneity in patient preferences makes it difficult, if not impossible, to identify a treatment that is preferred by all patients; there is currently no one-size-fits-all solution.

Our study has several limitations. First, while a strength of this review is the all-encompassing synthesis of preferences amongst CIS/RRMS patients, it did not include PPMS or SPMS patients. Therefore, the findings of this review may not be generalizable to PPMS or SPMS patients. However, PPMS/ SPMS patients might have different preferences anyhow due to a different disease course and this should be examined in a future review.

Second, we did not consult grey literature on patient treatment decisions or preferences, which may lead to selection bias.

Third, while a strength of this review is that primarily the needs and preferences of patients using injectable INF-β have been discussed, many studies have not yet explored the needs and preferences for oral therapies. With the recently available and more effective oral therapies, it is likely that reasons for treatment initiation, non-adherence and switch might be slightly different compared to the reasons reported in this review and should be explored further.

Fourth, it is difficult to conclude what the most important attribute is by ranking the top three attributes (like we have done) because the preference for an attribute depends on the levels of that attribute. The impact of an attribute may be due to the weights given to the attribute relative to other attributes or the scale values within the levels of an attribute (121). This is a common critique of the discrete choice methods (62,121). It is more informative to say something about the utility gain or loss within an attribute, for example within the attribute mode of administration, how much utility is gained from choosing a pill over an injectable. The BWS method does allow for respondents to compare utilities of the alternative levels of an attribute for them to decide what attributes levels they give the most and the least utility (62). Therefore, the BWS method can be a good alternative to DCE to elicit patient preferences for future studies.

A recently published systematic review by Webb et al. (2018) reported more stated preference studies than what we included in our review, which would suggest that our search strategy might have been too narrow. However, the review by Webb et al. focused mainly on the methodological limitations of stated preference studies in MS while we examined the findings of the studies.

CONCLUSION

In-depth knowledge of patient needs and preferences is required to optimize the treatment decision-making process for patients and physicians. This review has shown that few studies have examined the needs and preferences of RRMS patients when making their initial treatment decision. Future studies should therefore focus on the preferences of the patients recently diagnosed with MS. Many studies have focused on the reasons for non-adherence and discontinuation. While non-adherence may be a rational choice, it is also driven by forgetting to administer the treatment, and possible solutions to address this are mHealth/eHealth developments and patient management programs. Lastly, preference studies give valuable insight into what attributes of a treatment are important to patients and can thereby help to determine the best treatment for a patient as well as prevent non-adherence. For future preference studies in MS it is important to perform interviews and focus groups with patients to gather a more comprehensive list of patient-relevant attributes.

APPENDIX

Appendix A Full electronic search, Embase.com

('multiple sclerosis'/de OR ('multiple sclerosis' OR RRMS OR ms):ab,ti) AND ('patient attitude'/exp OR 'patient-reported outcome'/de OR motivation/de OR 'psychological aspect'/de OR 'coping behavior'/de OR 'shared decision making'/de OR 'adaptive behavior'/de OR 'patient comfort'/de OR 'personal experience'/de OR ((patient/de OR 'doctor patient relation'/de) AND (satisfaction/de OR perception/de OR 'decision making'/de OR 'incentives'/de OR 'psychology'/de)) OR ((patient* NEAR/3 (Preference* OR Perspective* OR need* OR attitude* OR satisf* OR psycholog* OR autonom* OR incentiv* OR disincentiv* OR comfort* OR dropout* OR drop*-out* OR behav* OR empower* OR participation* OR activat* OR involv* OR decision OR engage* OR choice* OR report* OR option* OR percept* OR persisten* OR experience OR experiences OR opinion*)) OR coping OR complian* OR noncomplian* OR adhere* OR nonadhere* OR motivat* OR ((psycholog* OR emotion* OR behav*) NEAR/3 (aspect* OR impact* OR adapt* OR adjust* OR handl*))):ab,ti) AND ('interferon'/de OR 'beta interferon'/de OR 'beta1 interferon'/de OR 'recombinant beta interferon'/de OR 'beta1a interferon'/de OR 'interferon beta serine'/de OR 'peginterferon beta1a'/de OR peginterferon/de OR 'peginterferon beta1a'/de OR 'glatiramer'/de OR 'teriflunomide'/de OR 'fumaric acid dimethyl ester'/de OR 'disease modifying therapy'/de OR 'disease modifying drug'/de OR 'disease modifying agent'/de OR 'immunomodulating agent'/de OR (interferon* OR ifn OR rifn OR peginterferon* OR ifn1a OR ifn1b OR ifnβ* OR ifnbeta* OR (disease NEAR/3 modif*) OR Avonex OR Betaferon OR Extavia OR Plegridy OR Rebif OR Glatiramer* OR Teriflunomid* OR Aubagio OR (Dimethyl* NEAR/3 fumar*) OR Tecfidera OR Betaseron* OR bg-12 OR ((early OR first-line OR firstline) NEAR/3 (treatment OR medication OR treat* OR therap*)) OR dmt OR dmts OR immunomodulat*):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim NOT ('case report'/de OR ('case report*'):ti)

Appendix B Study aim and adherence/ discontinuation rates for treatment adherence and discontinuation (D2a/ D2b)

Reference	Aim	Definition of adherence / persistence	D2a: Adherence rates D2b: Discontinuation rates
		Decision moment 2a	
(74)	Evaluate rates of adherence to prescribed DMTs and to explore factors affecting adherence amongst patients with RRMS	A: Not missing a single DMT injection within 4 weeks	75.0%
(75)	Evaluate adherence to, and effectiveness and convenience of, treatment in patients with RRMS using RebiSmart for self-injection of sc IFN b-1a	A: The proportion of expected injections completed during 12 months of treatment or until early discontinuation	97.1%
(76)	Evaluate the local tolerability, general safety, and efficacy of sc IFN β-1a in patients with RRMS and to assess treatment adherence	A: Patient takes his/her medication as instructed by the physician	79%
(77)	Determine factors associated with adherence to injectable DMTs in patients with RRMS	A: Not missing a single injection during the last 3 months	74.5%
(78)	Evaluating real-life long-term treatment adherence using RebiSmart in patients RRMS	A: Having administered at least 80% of the scheduled injections during the study period	80.6%
(79)	Identify factors that influence (non)-adherence in patients with RRMS	A: Not missing a single injection during the last 4 weeks	Month 1: 63% Month 2: 64%
(67)	To describe the perceived benefits and limitations of current DMT for MS, treatment adherence, impact on quality of life and daily living, and treatment expectations and needs	A: Having missed injections in the previous 3 months	73.8%
(80)	To assess the treatment adherence to DMTs in patients with RRMS.	A: Following the prescribed number of doses by the physician	Month 3: 97.3% Month 12: 93%
(68)	To explore patients' perspective on using DMTs	Not reported	Not reported
(71)	To understand what is means for people with RRMS to live with a chronic illness and use oral medication	Not reported	Not reported
(72)	To examine adherence to first-line DMTs in MS patients using the self-report Multiple Sclerosis Treatment Adherence Questionnaire	A: Not missing a single dose in the previous 28 days	76.5
(73)	To examine the seasonal variation of adherence to sc IFN β-1a through the RebiSmart device	A: The proportion of expected injections completed during 12 months of treatment	Per protocol set: 98.3% Full analysis set: 97.9%
		Decision moment 2b	
(84)	To determine long-term adherence to sc IFN β-1a treatment administered with the RebiSmart1 device in patients with RRMS	A: The proportion of expected injections completed during 12 months of treatment or until early discontinuation	34.5%

(85)	Explore the occurrence and reasons for stopping INFβ treatment and to assess the factors associated with long-term adherence in patients with RRMS	Not applicable	18.0%
(86)	Assess the relationship between patient readiness and adherence to self-injection and the relationship between mediating behavioural variables and adherence in patients with RRMS	A: Having used the therapy continuously for the duration of the study period	13.6%
(87)	Examine persistence and factors impacting persistence with the use of all injectable DMTs and the initially prescribed injectable DMT (GA or IFN-β) in adults with RRMS	P: the time-to-discontinuation of DMT	50.0%
(88)	To describe GA use and treatment persistence in a group of RRMS TN and TE (previously received INFs) patients	P: the time-to-discontinuation of DMT	32.2%
(75)	Evaluate adherence to, and effectiveness and convenience of, treatment in patients with RRMS using RebiSmart for self-injection of sc IFN b-1a	A: The proportion of expected injections completed during 12 months of treatment or until early discontinuation	12.8%
(78)	Evaluating real-life long-term treatment adherence using RebiSmart in patients RRMS	A: Having administered at least 80% of the scheduled injections during the study period	Not reported
(67)	To describe the perceived benefits and limitations of current DMT for MS, treatment adherence, impact on quality of life and daily living, and treatment expectations and needs	A: Having missed injections in the previous 3 months	17.8%
(89)	To examine perceived provider autonomy support among non-adherent RRMS patients who have discontinued DMT against medical advice	A: to have taken at least 80% of prescribed DMT over the previous 8 weeks	96%
(90)	To compare the proportion of patients discontinuing first-line injectable and oral DMT	Treatment discontinuation	23%
(81)	To investigate tolerability and satisfaction of teriflunomide	Treatment discontinuation	15.9%
(82)	To evaluate and compare treatment persistence between injectable and oral DMT to predict discontinuation	Treatment discontinuation at 12 months	20%
(83)	To describe long-term treatment persistence of GA under real-world conditions	P: treatment continuation after 5 years	54.7%

A: adherence, DMT: disease modifying treatment, GA: glatiramer acetate, IFN-β: beta interferon, P: persistence, RRMS: relapsing-remitting multiple sclerosis, sc: subcutaneous, TE: treatment experienced, TN: treatment naïve.

3

HEALTH-RELATED QUALITY OF LIFE OF MULTIPLE SCLEROSIS PATIENTS: A EUROPEAN MULTI-COUNTRY STUDY

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ABSTRACT

Background: Inconsistent use of generic and disease-specific health-related quality of life (HRQOL) instruments in multiple sclerosis (MS) studies limits cross-country comparability. The objectives: 1) investigate real-world HRQOL of MS patients using both generic and disease-specific HRQOL instruments in the Netherlands, France, the United Kingdom, Spain, Germany and Italy; 2) compare HRQOL among these countries; 3) determine factors associated with HRQOL.

Methods: A cross-sectional, observational online web-based survey amongst MS patients was conducted in June-October 2019. Patient demographics, clinical characteristics, and two HRQOL instruments: the generic EuroQOL (EQ-5D-5L) and disease-related Multiple Sclerosis Quality of Life (MSQOL)-54, an extension of the generic Short Form-36 (SF-36) was collected. Health utility scores were calculated using country-specific value sets. Mean differences in HRQOL were analysed and predictors of HRQOL were explored in regression analyses.

Results: In total 182 patients were included (the Netherlands: n=88; France: n=58; the United Kingdom: n=15; Spain: n=10; living elsewhere: n=11). Mean MSQOL-54 physical and mental composite scores (42.5, SD:17.2; 58.3, SD:21.5) were lower, whereas the SF-36 physical and mental composite scores (46.8, SD:22.6; 53.1, SD:22.5) were higher than reported in previous clinical trials. The mean EQ-5D utility was 0.65 (SD:0.26). Cross-country differences in HRQOL were found. A common predictor of HRQOL was disability status and primary progressive MS.

Conclusions: The effects of MS on HRQOL in real-world patients may be underestimated. Combined use of generic and disease-specific HRQOL instruments enhance the understanding of the health needs of MS patients. Consequent use of the same instruments in clinical trials and observational studies improves cross-country comparability of HRQOL.

BACKGROUND

Multiple sclerosis (MS) is a chronic disease with neurological dysfunction of the central nervous system, affecting 700,000 people in Europe and some 2.3 million people worldwide (122,123). While the survival of MS patients has improved (123), they still have lower health related quality of life (HRQOL) compared to the general population (124) and patients with other chronic diseases (18,19). HRQOL measures the impact of an illness or disease on the quality of life of patients as how they perceive it and its measurement helps to determine the effects of a treatment on HRQOL.

Many different generic or disease-specific HRQOL instruments have been used in MS-related randomized controlled trials (RCTs), observational studies and patient registries (125,126). Whilst generic instruments make it possible to compare HRQOL results to those of the general public and other diseases, disease-specific instruments can provide results that are more tailored to the disease in question (47). Commonly used generic instruments in MS clinical studies and economic evaluations are the Medical Outcomes Study Short Form-36 (SF-36) and the EuroQOL 5 dimensions questionnaire (EQ-5D) (47,125,127,128). A hybrid HRQOL instrument that combines aspects of the generic SF-36 with MS-specific domains, such as questions about bladder/bowel function and sexual function, is the Multiple Sclerosis Quality of Life (MSQOL)-54 instrument (129). While it is advisable to use both generic and disease-specific instruments to inform health technology assessment of treatments (45), it is uncommon to include both instruments in RCTs or observational studies (125). To be able to inform both healthcare professionals and policy makers about the HRQOL of MS patients outside a clinical setting, it is therefore interesting to collect so-called real-world data.

The use of diverse HRQOL instruments in different MS studies limits the comparability of outcomes between these studies (130). To the best of our knowledge, there has been no recent comprehensive European study of the HRQOL of MS patients in a real-world setting using both a generic and disease-specific HRQOL instrument. The aim of this study is threefold: 1.) to investigate the real-world HRQOL of patients with MS in several European countries including the Netherlands, France, the United Kingdom, Spain, Germany and Italy, 2.) to compare HRQOL among these countries, and 3.) determine factors associated with HRQOL.

METHODS

Study design

We performed a cross-sectional online survey between June and October 2019 in six European countries (the Netherlands, France, the United Kingdom, Spain, Germany and Italy). These countries were selected to give a representative overview of the HRQOL of the EU-5 and the Dutch MS patient population. Patients were recruited through the information channels of national patient societies and social media. Based on feasibility and the exploratory nature of the study (to investigate the current HRQOL of MS patients, and no hypothesis testing) we aimed to include 50 persons per country (i.e. non-probability sampling). In France the patients were also recruited by a MS specialist working at a MS centre in Paris. The study information and informed consent form could be downloaded by the patient. The research protocol was reviewed and approved by the Medical Research Ethics Committees of the Erasmus Medical Centre (MEC-2018-1636). Qualtrics XM software was used to perform the survey. The STROBE checklist for cross-sectional studies was used for reporting this study (131).

Inclusion criteria

Patients had to be ≥ 18 years old and have the diagnosis of clinically definite MS (including clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), or primary progressive MS (PPMS)). No restrictions were made on whether patients were currently

taking or had previously taken disease modifying therapies (DMTs). Participants required access to the internet.

Data collection

The online web-based survey consisted of three parts: 1) patient demographics and clinical characteristics; 2) the EQ-5D with five levels (EQ-5D-5L) to collect information about the patient's health state(128); and 3) the MSQOL-54 to collect information about the disease-related QOL (129). The survey took roughly 15-20 minutes to complete.

The survey was available in six languages and the participant was free to choose which language to use when completing it. Questions regarding demographics and clinical characteristics were translated from Dutch into the other languages by a professional translation agency and double-checked by native speakers. Official translations of the EQ-5D-5L and the MSQOL-54 were used.

Measures

Patients were asked to provide information on their age, country of residence (options: the Netherlands, France, the United Kingdom, Spain, Germany, Italy and 'living elsewhere'), nationality, gender, marital status and educational level. Clinical characteristics included the type of MS, age at diagnosis, disability and their current and previous treatment. Disability was self-reported using the Expanded Disability Status Scale (EDSS), an instrument to rate neurological impairments, with a total score ranging from 0 (normal) to 10 (death due to MS) (6).

The EQ-5D-5L is a standardized and validated HRQOL instrument (128,132) that yields a single generic measure of health to quantify HRQOL used in clinical and economic evaluations (125,133). The health states can be converted into a single "health utility" score, where 0 equals death and 1.0 equals perfect health. For France, the Netherlands and Spain the health utility scores were calculated using French, Dutch and Spanish country value sets, respectively (134–136). For the UK, the crosswalk value set was used (137,138). The value set used to calculate utility scores of patients living elsewhere was determined by the most commonly used language filled in by the patients living elsewhere.

The MSQOL-54 is a validated instrument with an adequate test-retest reliability, construct validity and internal consistency (129). The instrument consists of the generic SF-36 (127), extended with health concepts relevant for MS patients (129). It contains 52 QOL items that are divided across 12 scales (physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function) and two single items (satisfaction with sexual function and change in health) (129). Two summary scores, physical health composite score (PHCS) and mental health composite score (MHCS) are derived from a weighted combination of scale scores. Scale and composite scores range from 0-100, where a higher score indicates a better QOL (129). The SF-36 composite scores can be calculated from the MSQOL-54 (129) and have a mean of 50 (SD:10) in the general population (139).

Statistical analysis

Statistical analyses were performed with Stata 16.0. Analyses were stratified according to country of residence. Differences in mean scores across countries were calculated using the analysis of variance (ANOVA) test; if assumptions for the ANOVA were violated (we checked the distribution of the variables by plotting a histogram), the non-parametric Kruskal-Wallis test was used. Testing for a relationship between categorical variables was done using the chi-square test or the non-parametric Fishers exact test for small samples. Post-hoc analysis was done using either the Bonferroni correction or the Dunn's test. Statistical significance was defined as $p<0.05$.

Bivariate association of the EQ-5D-5L dimensions to EDSS was investigated with Spearman correlation coefficients. Univariate and multivariate analyses were conducted to examine the relationship between patient demographics and the EQ-5D-5L dimensions, health utility, the MSQOL-54 scales and the PHCS/MHCS. Covariates included in the multiple regressions were based on significance in the univariate analysis. A linear or logistic regression was performed for a continuous or categorical outcome variable, respectively. The stepwise backward selection method was used for the multivariate regression and variables were kept in the model based on significance.

RESULTS

The attempted sample size of 50 per country was not feasible in the UK, Spain, Germany and Italy given that patients were very difficult to recruit, therefore we ceased recruitment 5 months after the start of the study. A total of 281 patients were recruited and started the survey. Ninety-nine participants were dropped from the analysis since they did not finish the survey (n=55), did not give informed consent (n=39), had provided an age of diagnosis that was older than their current age (n=3), or were younger than 18 years (n=2). This left 182 participants for analysis.

Patient demographics can be found in Table 1. Patients were analysed based on country of residence (the Netherlands: n=88; France: n=58; the United Kingdom: n=15; living elsewhere: n=11; Spain: n=10). The total population had a median age of 43 years old and the average age at diagnosis was 34 years old. Roughly 80% were female and most participants (80%) had RRMS. There were no significant differences in patient demographics across the countries other than the age at diagnosis (range: 31.2-41.6 years) and educational level (an average of 52% having a university degree).

The results regarding current and past treatments can be found in the Appendix (Table A1). A total of 165 patients (90.8%) received DMT at one time or another; more than two-thirds were either currently taking a DMT (n=131, 72.0%) or had received it in the past (n=34, 18.9%). Of those currently taking a DMT, 44.7% were taking a first-line DMT, which was either an injectable (n=26; 19.9%) or an oral treatment (n=32; 24.4%). Over half of the patients currently taking a DMT were receiving a second-line therapy (n=73; 55.7%). A minority received oral treatment (n=20; 27.4%) and the majority received infusion therapy (n=52; 71.2%). Many of the patients receiving infusion therapy were taking ocrelizumab (n=39; 75%).

The DMT frequencies seen in the different countries were not significantly different, except for the use of INF-β 1a (p=0.018) and ocrelizumab (p=0.003) (Table A1). A cross-country difference was found regarding previous use of INF-β 1a (range: 6.7-27.6%), driven primarily by the French and Dutch populations. Furthermore, a cross-country difference was found regarding current use of ocrelizumab (range: 0.0-32.9%). Treatments used by less than 5% of the patients included INF-β 1b, cladribine and alemtuzumab.

	Total (n=182)	The Netherlands (n=88)	France (n=58)	The United Kingdom (n=15)	Spain (n=10)	Elsewhere (n=11)	P-value
Age, mean (±SD)	43.09 (10.53)	43.97 (10.27)	40.88 (10.57)	47.6 (9.39)	42.90 (11.37)	41.73 (12.08)	0.237[a]
Age at diagnosis, mean (±SD)	34.12 (10.36)	35.18 (10.3)	31.22 (9.53)	41.6 (10.17)	31.67 (11.04)	32.75 (9.84)	0.006[a]*
Time since diagnosis, mean (±SD)[c]	8.97 (7.8)	8.78 (7.33)	9.66 (8.61)	6 (4.31)	9.8 (9.5)	10.18 (927)	0.834[a]
Gender, n (%)							0.746[b]
Male	39 (21.43)	21 (23.86)	9 (15.52)	3 (20.00)	3 (33.00)	3 (27.27)	
Female	142 (78.02)	66 (75.00)	49 (84.48)	12 (80.00)	7 (70.00)	8 (72.73)	
Prefer not to say	1 (0.55)	1 (1.14)					
Type of MS, n (%)							0.649[b]
CIS	2 (1.10)		2 (3.45)				
RRMS	146 (80.22)	70 (79.55)	47 (81.03)	10 (66.67)	9 (90.00)	10 (90.91)	
PPMS	17 (9.34)	10 (11.36)	4 (6.90)	3 (20.00)	1 (10.00)	1 (9.09)	
SPMS	17 (9.34)	8 (9.09)	5 (8.62)	2 (13.33)			
EDSS, n (%)							0.070[b]
EDSS <= 2.5	45 (24.73)	12 (13.64)	20 (34.48)	3 (20.00)	6 (60.00)	4 (36.36)	
EDSS 3 - 6.5	35 (19.23)	15 (17.05)	12 (20.69)	4 (26.67)	2 (20.00)	2 (18.18)	
EDSS >= 6	26 (14.29)	14 (15.91)	6 (10.34)	6 (40.00)	2 (20.00)		
Unknown	58 (31.87)	30 (34.09)	20 (34.48)	2 (13.33)		4 (36.36)	
Missing	18 (9.89)	17 (19.32)				1 (9.09)	
Marital status, n (%)							0.986[b]
Single	36 (19.78)	17 (19.32)	13 (21.41)	3 (20.00)	1 (10.00)	2 (18.18)	
Partnered	42 (23.08)	21 (23.86)	13 (21.41)	5 (33.33)	2 (20.00)	1 (9.09)	
Married	96 (52.75)	44 (50.00)	30 (51.72)	7 (46.67)	7 (70.00)	8 (72.73)	
Divorced	7 (3.85)	5 (5.68)	2 (3.45)				
Widowed	1 (0.55)	1 (1.14)					
Educational level, n (%)							0.000[b]
Primary education	1 (0.55)				1 (10.00)		
Secondary education	13 (7.14)	9 (10.23)		3 (20.00)		1 (9.09)	
Vocational/technical education	67 (36.82)	44 (50.00)	14 (24.14)	4 (26.67)	3 (30.00)	2 (18.18)	
University	95 (52.20)	35 (39.77)	41 (70.69)	6 (40.00)	5 (50.00)	8 (72.73)	
Other	6 (3.30)		3 (5.17)	2 (13.33)	1 (10.00)		
Nationality, n (%)							
British	14 (7.69)			14 (93.33)			

French	59 (32.42)		57 (98.28)			2 (18.18)
Dutch	91 (50.00)	87 (98.86)	1 (1.72)			3 (27.27)
Spanish	9 (4.95)				9 (90.00)	
Other	9 (4.95)	1 (1.14)		1 (6.67)	1 (10.00)	6 (54.55)

Table 1 Patient demographics.

CIS: clinically isolated syndrome, EDSS: Expanded Disability Status Scale, MS: multiple sclerosis, PPMS: primary progressive MS, RRMS: relapsing-remitting MS, SPMS: secondary progressive MS. [a]: Kruskal-Wallis test, [b]: Fisher's exact test, [c]: Time since diagnosis was calculated by subtracting the age at diagnosis from the current age, *Significant difference in mean age at diagnosis between France and the United Kingdom (p=0.002) using Dunn's test and Bonferroni correction.

EQ-5D-5L

The total mean health utility score was 0.65 (SD:0.26) (Table 2). Overall, one-third of all patients had moderate problems with mobility (n=57; 31.3%) and 44% had moderate problems with usual activities. A majority had slight to moderate pain and discomfort (n=62; 34.17% and n=60; 32.9%). Generally, the patients had no problems with self-care (n=117; 64.3%) or anxiety and depression (n=75; 41.2%).

Given the country-specific tariffs, there were statistically significant differences in utility between the countries (range: 0.48-0.78; $p<0.001$) (Table 2). However, once calculated using only the Dutch tariff, this was no longer the case (range: 0.48-0.73; $p=0.012$) (results not shown). No statistical between-country differences were found amongst the EQ-5D-5L dimensions (Table 2).

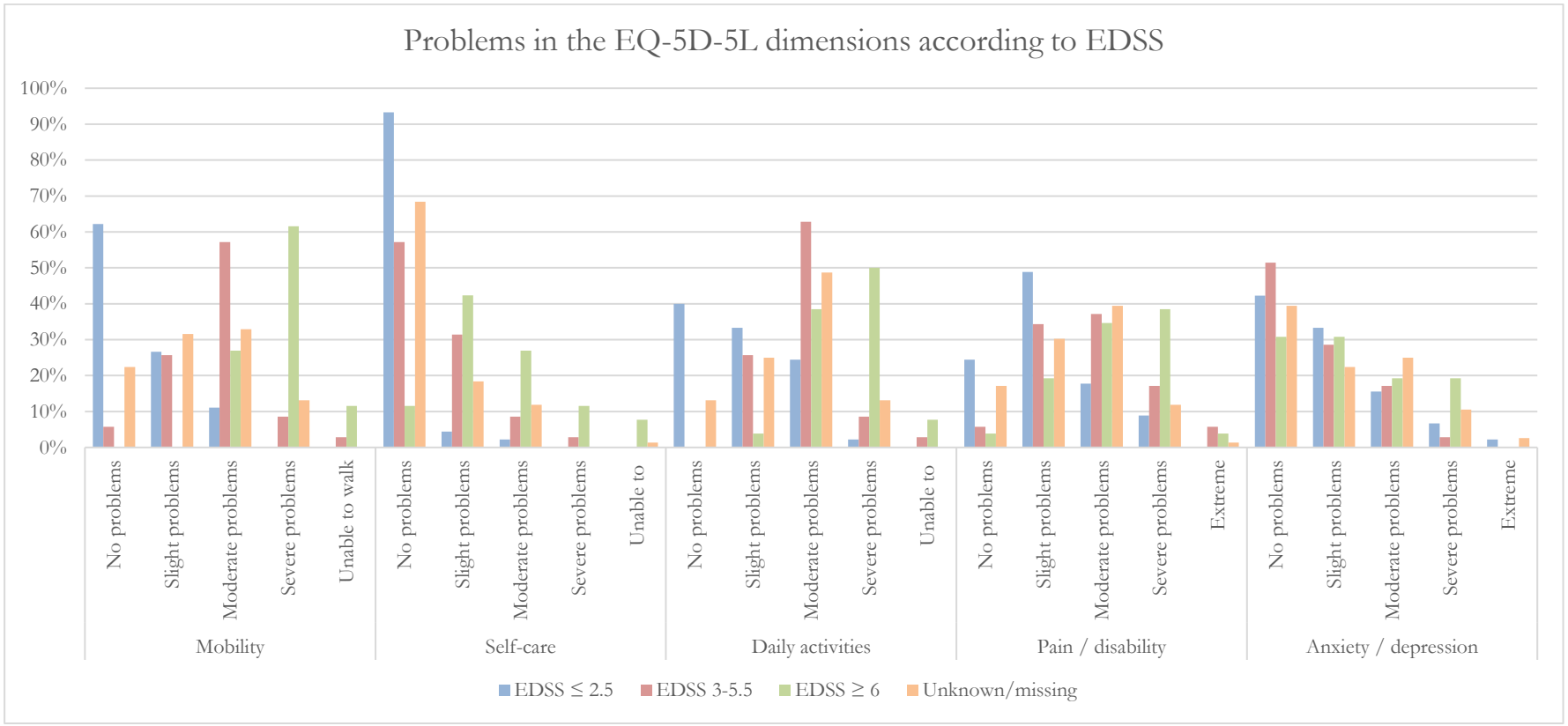
Patients with mild disability (EDSS ≤2.5) generally had no problems with mobility (n=28; 62.2%) or self-care (n=42; 93.3%) (Figure 1). However, almost 60% had slight to moderate problems with daily activities, and 48.9% suffered from slight pain. The majority were not anxious or depressed (n=19; 42.2%). Patients with greater disability (EDSS 3-5.5 and ≥ 6) were more likely to have moderate to severe problems in mobility, daily activities and pain/discomfort. However, disability was not associated with anxiety/depression. Furthermore, there was a strong and significant correlation of the EQ-5D-5L domains mobility, self-care and usual activities to disability (Appendix Table A2). Pain/ discomfort had a moderate significant correlation, whereas anxiety/depression had a weak though non-significant correlation to disability.

Table 2 Problems in the EQ-5D-5L dimensions and health utility of the total study population and according to country of residence

	Total (n=182)	The Netherlands (n=88)	France (n=58)	The United Kingdom (n=15)	Spain (n=10)	Elsewhere (n=11) [c]	P-value
Mobility, n (%)							0.086[b]
No problems	47 (25.82)	15 (17.05)	21(36.21)	1(6.67)	6 (60.00)	4 (36.36)	
Slight problems	45 (24.73)	25 (28.41)	12 (20.69)	3 (20.00)	1 (10.00)	4 (36.36)	
Moderate problems	57 (31.32)	29 (32.95)	16 (27.59)	6 (40.00)	3 (30.00)	3 (27.27)	
Severe problems	29 (15.93)	17 (19.32)	7 (12.07)	5 (33.33)			
Unable to walk	4 (2.20)	2 (2.27)	2 (3.45)				
Self-care, n (%)							0.094[b]
No problems	117 (64.29)	50 (56.82)	44 (75.86)	5 (33.33)	9 (90.00)	9 (81.82)	I
Slight problems	38 (20.88)	21 (23.86)	10 (17.24)	4 (26.67)	1 (10.00)	2 (18.18)	
Moderate problems	20 (10.99)	12 (13.64)	3 (5.17)	5 (33.33)			
Severe problems	4 (2.20)	3 (3.41)		1 (6.67)			
Unable to wash or dress myself	3 (1.65)	2 (2.27)	1 (1.72)				
Usual activities, n (%)							0.254[b]
No problems	28 (15.38)	10 (11.36)	11 (18.97)	1 (6.67)	3 (30.00)	3 (27.27)	
Slight problems	44 (24.18)	19 (21.59)	16 (27.59)	2 (13.33)	4 (40.00)	3 (27.27)	
Moderate problems	80 (43.96)	39 (44.32)	27 (46.55)	8 (53.33)	2 (20.00)	4 (36.36)	
Severe problems	27 (14.84)	18 (20.45)	4 (6.90)	3 (20.00)	1 (10.00)	1 (9.09)	
Unable to do my usual activities	3 (1.65)	2 (2.27)		1 (6.67)			
Pain / discomfort, n (%)							0.529[b]
No pain	27 (14.84)	17 (19.32)	5 (8.62)	1 (6.67)	3 (30.00)	1 (9.09)	
Slight pain	62 (34.07)	27 (30.68)	23 (39.66)	4 (26.67)	3 (30.00)	5 (45.45)	
Moderate pain	60 (32.97)	25 (28.41)	21 (36.21)	6 (40.00)	4 (40.00)	4 (36.36)	
Severe pain	29 (15.93)	18 (20.45)	7 (12.07)	3 (20.00)		1 (9.09)	
Extreme pain	4 (2.20)	1 (1.14)	2 (3.45)	1 (6.67)			
Anxiety / depression, n (%)				.			0.061[b]
No problems	75 (41.21)	48 (54.55)	14 (24.14)	6 (40.00)	4 (40.00)	3 (27.27)	
Slight problems	50 (27.47)	19 (21.59)	21 (36.21)	4 (26.67)	3 (30.00)	3 (27.27)	
Moderate problems	37 (20.33)	14 (15.91)	12 (20.69)	4 (26.67)	2 (20.00)	5 (45.45)	
Severe problems	17 (9.34)	7 (7.95)	8 (13.79)	1 (6.67)	1 (10.00)		
Extremely anxious/depressed	3 (1.65)		3 (5.17)				
Health utility, mean (SD)	0.65 (0.26)	.58 (0.28)	.76 (0.22)	0.48 (0.25)	0.78 (0.14)	0.68 (0.19)	<0.001[a]*

SD: standard deviation. [a]: Kruskal-Wallis test, [b]: Fisher's exact test, [c]: Index calculated with the Dutch tariff since n=8/11 filled out the Dutch version of the survey. *: Significant difference in health utility scores between France and the Netherlands ($p<0.001$), France and the United Kingdom ($p<0.001$), the United Kingdom and Spain ($p=0.021$), based on Dunn's test and Bonferroni correction.

Figure 1 Problems in the EQ-5D-5L dimensions according to disability status of the total study population



EDSS: Expanded Disability Status Scale, EQ-5D-5L: EuroQol 5-dimensions 5 levels.

MSQOL-54 and SF-36

The results of the MSQOL-54 and SF-36 are presented in Table 3. The mean MSQOL-54 physical health composite score (MSQOL-54 PHCS) and mental health composite scale (MSQOL-54 MHCS) for the total population was 42.5 (SD: 17.2) and 58.3 (SD: 21.5), respectively. The mean MSQOL-54 PHCS differed significantly between countries (range: 31.9-55.6, p=0.017). In contrast, no significant difference between countries was found on the MSQOL-54 MHCS (range: 51.9-65.9, p=0.06). The mean SF-36 physical composite score (SF-36 PCS) and mental composite score (SF-36 MCS) for the total population was 46.8 (SD: 22.6) and 53.1 (SD: 22.45), respectively. Both scores differed significantly between countries (PCS: range 32.9-65.1, p=0.007; MCS: range 44.5-65.7, p=0.016).

Regression analyses

Table 4 shows the results of the analyses to examine the relationship between patient demographics and the health utility, PHCS and MHCS scores. Multivariate analysis found that age, age at diagnosis, marital status and current line of treatment were not associated with utility, PHCS and MHCS. PPMS was independently associated with lower utility, PHCS and MHCS. Furthermore, moderate to severe disability (EDSS 3-9.5) and unknown disability was independently associated with lower utility and PHCS. After correction for other characteristics, French patients reported a higher utility than other patients, while Dutch and Spanish patients reported a higher PHCS score.

Additional univariate and multivariate models for the EQ-5D-5L dimensions and utility, MSQOL-54 scales and composite scores are shown in the Appendix (Tables A3, A4).

Table 3 The MSQOL-54 and SF-36 scores of the total study population and according to country of residence

	Total (n=182)	The Netherlands (n=88)	France (n=58)	The United Kingdom (n=15)	Spain (n=10)	Elsewhere (n=11)	P-value [a]
MSQOL-54							
Physical health composite score, mean (SD)	**42.54 (17.15)**	**42.07 (16.72)**	**42.14 (16.73)**	**31.89 (15.18)**	**55.65 (16.98)**	**49.97 (17.61)**	0.017[I]
Physical function	54.86 (30.63)	49.55 (29.43)	63.85 (30.35)	28.74 (26.65)	72.00 (18.74)	70.00 (24.49)	<0.000[II]
Health perception	38.8 (22.56)	38.42 (24.19)	35.93 (18.73)	34.53 (18.59)	54.17 (22.62)	48.75 (27.48)	0.177
Energy/ fatigue	35.88 (19.86)	38.95 (20.79)	30.41 (17.51)	27.47 (12.18)	44.20 (21.05)	44.00 (22.77)	0.022
Role limitations – physical	30.77 (37.35)	26.04 (34.06)	35.06 (39.70)	16.67 (30.86)	60.00 (44.41)	38.64 (39.31)	0.043[III]
Pain	65.81 (25.7)	68.22 (25.48)	63.16 (26.08)	53.89 (30.1)	72.00 (15.03)	71.06 (24.18)	0.388
Sexual function combined	65.89 (27.13)	70.17 (26.65)	60.49 (24.76)	49.4 (32.44)	76.67 (26.88)	71.22 (26.45)	0.013
Sexual function male	65.57 (29.27)	63.34 (30.64)	68.53 (26.61)	47.23 (41.12)	80.56 (26.79)	75.01 (25.00)	0.769
Sexual function female	65.97 (26.64)	72.19 (25.26)	59.01 (24.41)	50 (32.06)	75.00 (28.87)	69.80 (28.50)	0.008[IV]
Health distress	54.95 (24.59)	56.33 (24.56)	50.34 (24.88)	53 (22.82)	69.50 (28.03)	57.73 (19.02)	0.251
Mental health composite score, mean (SD)	**58.26 (21.48)**	**62.15 (19.89)**	**51.93 (22.34)**	**54.98 (23.1)**	**65.98 (25.00)**	**57.64 (17.83)**	0.060[V]
Health distress	54.95 (24.59)	56.33 (24.56)	50.34 (24.88)	53 (22.82)	69.50 (28.03)	57.73 (19.02)	0.251
Overall quality of life	58.51 (19.06)	60.98 (18.48)	55.83 (20.07)	48.11 (19.05)	64.08 (14.94)	61.29 (17.08)	0.082
Emotional well-being	62.53 (21.01)	68.09 (18.45)	53.36 (22.06)	60 (22.32)	66.00 (24.96)	66.64 (13.84)	0.003[VI]
Role limitations – emotional	57.04 (43.51)	63.22 (42.54)	47.95 (42.73)	53.33 (46.80)	70.00 (42.89)	48.48 (47.99)	0.195
Cognitive function	54.52 (24.85)	56.19 (24.06)	51.18 (23.85)	58.00 (32.34)	58.50 (23.46)	50.45 (28.24)	0.610
Change in health	44.23 (26.29)	47.16 (29.47)	43.97 (23.09)	31.67 (19.97)	52.5 (27.51)	31.82 (11.68)	0.079
Satisfaction with sexual function	52.63 (33.47)	51.42 (36.03)	51.29 (28.65)	40.38 (36.14)	72.5 (34.26)	65.91 (25.67)	0.121
SF-36							
Physical composite scale, mean (SD)	46.82 (22.60)	44.71 (21.25)	48.56 (22.30)	32.90 (19.38)	65.10 (22.34)	56.9 (26.05)	0.007[VII]
Mental composite scale, mean (SD)	53.11 (22.45)	57.02 (21.09)	46.40 (22.57)	44.54 (22.23)	65.69 (25.22)	57.25 (20.17)	0.016[VIII]

MSQOL-54: Multiple Sclerosis Quality of Life -54 instrument, SF-36: Medical Outcomes Study Short Form-36. [a]: Kruskal-Wallis test and post-hoc analysis using Dunn's test and Bonferroni correction. [I] Significant difference in mean physical health composite score between the United Kingdom and Spain (p=0.007); [II] Significant difference in mean physical

function scores between the United Kingdom and France, the United Kingdom and elsewhere and the United Kingdom and Spain (p=<0.000 for all three situations), and France and the Netherlands (p=0.04); [III] Significant differences in mean role limitations physical between the United Kingdom and Spain (p=0.029); [IV] Significant difference in mean sexual function female between France and elsewhere (p=0.014); [V] Significant difference in mean mental health composite score between France and the Netherlands (p=0.046); [VI] Significant difference in mean emotional well-being score between France and the Netherlands (p<0.000). [VII] Sig difference between the United Kingdom and Spain (p=0.003), almost reaching significance difference between the United Kingdom and elsewhere (p=0.057), and the Netherlands and Spain (p=0.059); [VIII] Almost reaching sig difference between France and Spain (p=0.058). The sample size varied somewhat across the scales and the scores were calculated by excluding missing data(129). For 27 questions the range of missing data was 0.55-2.75% (n=1 to n=5). Additionally, the range of missing data for four out of five health perception scale questions was higher (n=20 to n=54; 14.83%-29.67%).

Missing data: The sample size varied somewhat across the domains, the composite scores were calculated from the domains by excluding missing data. Missing data were found in physical health function question 3 (0.55%, n=1 from the UK), physical health function question 5 (0.55%, n=1 from FR), physical health function question 8 (1.65%, n=3 from the NL), physical health function question 10 (0.55%, n=1 from the NL), health perceptions question 34 (25.27%, n=4, n=7, n=31, n=2, and n=2 from the UK, FR, NL, SP and elsewhere, respectively), health perceptions question 35 (10.99%, n=3, n=6, n=9, n=2 from the UK, FR, NL and SP country of residence, respectively), health perceptions question 36 (29.67%, n=3, n=15, n=30, n=4, n=2 from the UK, FR, NL, SP and elsewhere, respectively), health perceptions question 37 (14.83%, n=2, n=12, n=11, n=4, n=2 from the UK, FR, NL and SP country of residence, respectively), energy/fatigue question 23 (0.55%, n=1 from SP), energy/fatigue question 27 (0.55%, n=1 from FR), energy/fatigue question 29 (1.10%, n=1, n=1 from FR and NL respectively), energy/fatigue question 32 (1.65%, n=3 from FR), role limitations physical question 13 (1.10%, n=2 from FR), role limitations physical question 14 (0.55%, n=2 from NL), role limitations physical question 15 (0.55%, n=1 from NL), role limitations physical question 16 (1.10%, n=2 from NL), sexual function male (0.55%, n=1 from NL), sexual function female (0.55%, n=1 from UK), satisfaction with sexual function (1.10%, n=2 from UK), health distress question 39 and 40 (0.55%, n=1 from NL in both cases), overall quality of life (0.55%, n=1 from FR), emotional well-being question 28 (2.20%, n=1, n=2, n=1 from FR, NL and elsewhere, respectively), emotional well-being question 30 (0.55%, n=1 from FR), role limitations emotional question 17 (1.10%, n=1, n=1 from FR and NL, respectively), role limitations emotional question 18 (1.65%, n=2, n=1 from FR and NL, respectively), role limitations emotional question 19 (2.20%, n=2, n=2 from FR and NL, respectively), cognitive function question 42 (0.55%, n=1 from SP), cognitive function question 43 (1.10%, n=2 from ES), cognitive function question 44 (1.65%, n=1, n=1, n=1 from FR, NL and SP, respectively), cognitive function question 45 (2.75%, n=1, n=4 from FR and SP, respectively).

Table 4 Linear regression estimates: predictors of health utility and the MSQOL-54 composite scores of the total study population

	Health utility Univariate	**Health utility** Multivariate [a]	**PHCS** Univariate	**PHCS** Multivariate	**MHCS** Univariate	**MHCS** Multivariate
Age (years)	-0.006 (0.002)***		-0.257 (0.120)**		0.149 (0.154)	
Age at diagnosis (years)	-0.007 (0.002)**		-0.159 (0.124)		-0.010 (0.156)	
Time since diagnosis (years)	-0.000 (0.003)		-0.190 (0.163)		0.282 (0.205)	
Gender (female vs. male)	0.055 (0.047)		0.482 (3.098)		-3.742 (3.883)	
Marital status						
Single						
Partnered	0.119 (0.061) *		3.770 (3.923)		6.816 (4.958)	
Married	0.084 (0.052)		5.372 (3.384)		7.889 (4.289)*	
Divorced	-0.070 (0.110)		-4.081 (7.097)		9.444 (8.921)	
Widowed	0.171 (0.280)		-3.549 (17.383)		16.736 (21.807)	
Educational level						
Primary education						
Secondary education	-0.296 (0.274)		-38.651 (17.450)**		-23.068 (22.460)	
Vocational/technical education	-0.223 (0.266)		-33.782 (16.940)**		-25.104 (21.803)	
University	-0.119 (0.265)		-27.890 (16.905)		-24.458 (21.759)	
Other	-0.160 (0.285)		-32.622 (18.163)*		-24.722 (23.377)	
Country of residence						
United Kingdom						
France	0.281 (0.073)***	0.131(0.034)***	10.251 (4.968)**		-3.051 (6.137)	
The Netherlands	0.098 (0.070)		10.174 (4.800)**	5.364 (2.445)**	7.168 (5.912)	
Spain	0.293 (0.103)***		23.758 (6.907)***	11.074 (5.002)***	11.000 (8.633)	
Elsewhere	0.195 (0.100)*		18.075 (6.722)***		2.663 (8.395)	
Type of MSI						
CIS / RRMS						
PPMS	-0.387 (0.062)***	-0.215 (0.058)***	-21.055 (4.219)***	-13.024 (4.208)***	-17.066 (5.343)***	-17.815 (5.326)***
SPMS	-0.143 (0.062)**		-9.204 (4.105)**		7.183 (5.343)	
EDSS						
EDSS <= 2.5						
EDSS 3 -5.5	-0.161 (0.051)***	-0.129 (0.048)***	-12.436 (3.482)***	-11.320 (3.419)***	-1.415 (4.847)	
EDSS >= 6	-0.485 (0.056)***	-0.383 (0.056)***	-25.362 (3.854)***	-21.194 (3.997)***	-7.789 (5.294)	
Unknown / missing	-0.151 (0.043)***	-0.113 (0.040)***	-11.534 (2.906)***	-10.677 (2.851)***	-7.121 (4.064)*	
Current line of treatment						
Treatment naive						
1st-line DMT	0.259 (0.071)***		10.778 (4.785)**		1.709 (5.970)	
2nd-line DMT	0.115 (0.069)		4.477 (4.677)		1.259 (5.844)	
Treatment experience but currently no DMT	0.127 (0.077)*		4.857 (5.137)		3.450 (6.429)	

**** p<0.01, ** p<0.05, * p<0.1 Standard errors are in parenthesis*

CIS: clinically isolated syndrome, DMT: disease modifying therapy, EDSS: Expanded Disability Status Scale, MHCS: mental health composite score, PHCS: physical health composite score, PPMS: primary progressive multiple sclerosis, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis. [a] Results show the regression with utility calculated using the country-specific tariffs. The multivariate regression was re-run calculating the utility with only the Dutch tariffs; country of residence was no longer a significant variable (Appendix Table A3).

DISCUSSION

The aim of this study was to examine real-world HRQOL of patients with MS in several European countries. The generic health utility instrument (the EQ-5D-5L) and the hybrid disease-specific MSQOL-54 (including the SF-36) instruments were used to calculate HRQOL. Compared to previous research, our results indicate that the HRQOL of MS patients may have been overestimated. We found a relatively low health utility score, with no between-country differences amongst the EQ-5D-5L dimensions. Somewhat low HRQOL was found using the MSQOL-54 with between-country differences. Furthermore, disability status and PPMS is negatively correlated with HRQOL.

The mean EQ-5D utility score (0.65 ± 0.26 SD) in our population was lower than the scores (range: 0.69 - 0.78) reported in other multi-country studies (140–142). Previous MS studies have used the older EQ-5D-3L method, rather than the newer EQ-5D-5L (140–143). However, the EQ-5D-5L significantly increases sensitivity, reliability and has less of a ceiling effect than the EQ-5D-3L (132). Given that previous studies used the older EQ-5D-3L method to calculate utilities this limits the comparability. Nonetheless, a similar trend is seen regarding disability and problems experienced in the dimensions. For example, the correlation of EQ-5D-3L domains to EDSS found by the European observational study by Eriksson et al (2019) are of the same magnitude to ours (the coefficients for mobility: 0.77 vs 0.83; self-care 0.67 vs 0.68; usual activities: 0.64 vs 0.73; pain/discomfort: 0.37 vs 0.46; anxiety/depression: 0.13 vs 0.06) (143). As such, patients are more likely to suffer from problems with mobility, self-care, daily activities and pain/discomfort with increasing disability. Regarding anxiety and depression, MS patients did not seem to experience increasing problems with increasing disability.

Our European population had a somewhat higher mean SF-36 physical component summary score (46.8 SE:1.7) and mental component summary score (53.11 SE:1.6) than most previously published DMT studies. The CONFIRM and DEFINE study, examining HRQOL while taking dimethyl fumarate, found mean SF-36 PCS and MCS of 43.1 and 47.2, and 43.4 and 45.3, respectively (140,141). Also, the CARE-MS I and II trials (treatment naïve and treatment experienced patients receiving either INF-β 1a or alemtuzumab), found SF-36 composite scores higher than our study (PCS range: 43.9 - 46.5; MCS range: 42.4 - 48.3) (142). Even after the use of DMT treatment, the trials found lower composite scores compared to our results (140–142). This is somewhat in contrast to the review article by Jongen (2017), whom found that in clinical trials and observational studies DMT treatment may have a positive effect on HRQOL in RRMS patients (125), however it is less clear what the HRQOL is after such interventions. This may suggest that, based on the SF-36, real-world HRQOL of patients is more favourable than during a clinical trial.

The mean MSQOL-54 composite scores (PHCS: 42.5 SE:1.3; MHCS: 58.2 SE:1.6) in our European population were 10-20 points lower than scores reported in previous observational studies (144–148). For example, a European observational phase 4 study including 284 patients from the Netherlands, Belgium, Luxembourg and the United Kingdom, found mean MSQOL-54 PHCS and MHCS scores of 56.6 and 57.2 (148). Lower scores to ours may be due to population differences. The phase 4 study had a younger patient population (mean age 38.6 vs 43.1 years), less time since their RRMS diagnosis (3.5 vs 8.9 years) and less disability (mean EDSS 2.4 vs 3.5). Moreover, a 10-year HRQOL observational study with 77 ambulatory MS patients in Finland found PHCS of 63.9 (SE:2.1) and MHCS 73.6 (SE: 2.2) (147). Again, differences may be due to patient demographics, while the patients included in Finland were somewhat older at baseline (mean age 47 vs 43 years old), the majority of patients had less disability (70% of patients had EDSS 0-3).

Disease-specific measurements are more extensive and have greater sensitivity to changes, meaning it can detect HRQOL differences between patients (125). When correcting for patient characteristics, disability severity is negatively correlated with both health utility and the MSQOL-54 PHCS, however not with MHCS. The correlation between disease severity and lower utility or

physical health has been examined extensively (24,149,150), along with the negative effect of PPMS on HRQOL (151,152). Though one might expect that increasing disability will lead to lower mental health, this was not found, neither in the correlation of EQ-5D dimensions to EDSS or in the multivariate regression analysis. Symptoms such as depression, fatigue and anxiety are commonly known to have a negative effect on HRQOL (152,153). The psychological components of MS are just as important as the physical symptoms when managing HRQOL (154), though perhaps more difficult to target.

We want to inform physicians and policy makers that it is useful to include HRQOL instruments in clinical practice and in clinical trials. The use of such instruments in clinical practice enables physicians to know what dimensions of HRQOL to target. As such, it is possible to set up a personalized treatment plan, together with the patient, based on the HRQOL results (153). Moreover, the use of HRQOL instruments in clinical care has shown significant benefits to the care given to patients (153). Furthermore, we want to address the importance of measuring health utility and disease-specific HRQOL as end-points in clinical trials. Instruments such as the EQ-5D-5L and MSQOL-54 are able to quantity the potential added value of the new treatment or technology under examination, from the patient's perspective, in terms of HRQOL (155). This information is needed to perform a health technology assessment and the subsequent economic evaluation, which in turn is essential for health policy makers to decide on reimbursement decisions and allowing the treatment or technology to enter the market (125,156).

Limitations

There are various limitations to our study worth noting The design of this study was to examine HRQOL in Europe, and not between-country differences. However, post-hoc analysis revealed some between-country differences in HRQOL. Possible explanations of between country differences in HRQOL may be explained differing healthcare systems, the recruitment method and small samples in the UK and Spain. The healthcare systems of the examined countries differ, thereby possibly affecting the quality of care received by patients. Patients were recruited via the information channels of national patient societies, social media and via an MS specialist in France. Therefore, we had no control over how and to whom the patient societies reached out too, or the reach of our social media channels within the MS community. It is possible that the patient societies differed in how actively they promoted the study, leading to selection bias. Furthermore, the small samples from the United Kingdom and Spain limits their representability of the HRQOL status of those two countries, thus caution is needed when making statements on their HRQOL. Since we had small samples, we did not perform regressions per country. If larger samples had been recruited this may have given insight into possible country differences. Future studies should be designed to specifically examine cross-country differences and controlling for more information than we have included in this study.

Many disease-specific HRQOL instruments have been developed since the introduction of the MSQOL-54 in 1995, such as the Functional Assessment of MS (FAMS), the Hamburg Quality of Life Questionnaire in MS (HAQUAMS), the MS Impact Scale-29 (MSIS-29) and the MS International Quality of Life questionnaire (MusiQoL) to name a few (125), each focussing on a variety of MS-related domains. Though perhaps more relevant when examining only disease-specific HRQOL we did not find them suitable for this study. A deliberate choice was made to use the hybrid MSQOL-54 given that it is an extension of the generic SF-36, enabling comparability to other diseases. However, they are useful when examining a specific MS-specific HRQOL domain, and future researchers should include them when deemed necessary.

One MS centre in France was involved in the data collection and this may have led to sampling bias. This reduces the comparability of the French patients to patients in the other countries, although it is comparable to a previous French multicentre study by Lebrun-Frenay et al. (2017). For example, both studies found that patients were in their early thirties when diagnosed, at least 50% of the patients had a university degree and the type of DMT used was similar (157).

The similarities in the patient demographics show that similar recruitment methods lead to comparable patient populations, thereby validating the results of the study. Our findings give more in depth knowledge about the combined generic and disease-specific HRQOL status of French MS patients since Lebrun-Frenay and colleagues only examined health utility using the EQ-5D-3L.

Three patients (other than patients living elsewhere) filled out the survey in a language that differed from the official language of their country of residence which may have impacted health utility results (since health utility is somewhat influenced by the choice of national value set) (135,158). All patients were analysed based on country of residence, not on their nationality or user language of the survey (which may have differed across participants). However, since only involved three patients were involved, this had no major impact on the results.

Since the EDSS was self-reported, it is possible that some patients incorrectly estimated their EDSS due to a lack of understanding of the scale, despite having the option to indicate that they did not know it. However, the negative association we observed between EDSS and HRQOL suggests that this issue had a limited effect on the results. Nevertheless, caution is needed when interpreting the results. At the time of data collection the self-reported disability status scale (SRDSS) as a proxy measure to estimate EDSS was not yet available, however such a measure may be useful for self-assessment of disability in an online questionnaire environment (159). Another measure that we could have employed was the self-reported Patient Determined Disease Steps, although this would have limited comparisons with other studies (160).

CONCLUSIONS

Our results indicate that, till now, the effects of MS on HRQOL may have been underestimated in real-world MS patients. The combined use of both generic and disease-specific HRQOL instruments as outcome measures in clinical trials and observational studies allow for a deeper understanding about specific health needs of MS patients. To enhance the comparability of cross-country data from RCTs, observational studies, or patient registries it is essential to use the same instruments consequently. This study has made a first attempt to do so across Europe, however a more collective effort has to be made by all persons involved in health care research.

APPENDIX

Appendix A1 Current and past disease modifying treatment of the total study population and according to country of residence

	Total (n=182)	The Netherlands (n=88)	France (n=58)	The United Kingdom (n=15)	Spain (n=10)	Elsewhere (n=11)	P-value[a]
INJECTABLES							
INF-β 1a (Avonex), n (%)							0.018
I am currently using this treatment	7 (3.85)		4 (6.90)	1 (6.67)		2 (18.18)	
I have used this treatment in the past	38 (20.88)	16 (18.18)	16 (27.59)	1 (6.67)	2 (20.00)	3 (27.17)	
I have never used this treatment	137 (75.27)	72 (81.82)	38 (65.52)	13 (86.67)	8 (80.00)	6 (54.55)	
INF-β 1a (Rebif) , n (%)							0.292
I am currently using this treatment	6 (3.30)	1 (1.14)	3 (5.17)	1 (6.67)	1 (10.00)		
I have used this treatment in the past	40 (21.98)	19 (21.59)	12 (20.69)	2 (13.33)	2 (20.00)	5 (45.55)	
I have never used this treatment	136 (74.73)	68 (77.27)	43 (74.14)	12 (80.00)	7 (70.00)	6 (54.55)	
PegINF-β 1a (Plegridy), n (%)							0.163
I am currently using this treatment	5 (2.75)	2 (2.27)	1 (1.72)		2 (20.00)		
I have used this treatment in the past	11 (6.04)	8 (9.09)	2 (3.45)		1 (10.00)		
I have never used this treatment	166 (91.21)	78 (88.64)	55 (94.83)	15 (100.00)	7 (70.00)	11 (100.00)	
INF-β 1b (Extavia), n (%)							0.775
I have used this treatment in the past	3 (1.65)	1(1.14)	2 (3.45)				
I have never used this treatment	179 (98.35)	87 (98.86)	56 (96.55)	15 (100.00)	10 (100.00)	11 (100.00)	
GA (Copaxone), n (%)							0.290
I am currently using this treatment	9 (4.95)	4 (4.55)	4 (6.90)			1 (9.09)	
I have used this treatment in the past	54 (29.67)	28 (31.82)	21 (36.21)	1 (6.67)	2 (20.00)	2 (18.18)	
I have never used this treatment	119 (65.38)	56 (63.64)	33 (56.90)	14 (93.33)	8 (80.00)	8 (72.73)	
ORAL							
DMF (Tecfidera), n (%)							0.877
I am currently using this treatment	18 (9.89)	8 (9.09)	6 (10.34)	3 (20.00)		1 (9.09)	
I have used this treatment in the past	23 (12.64)	13 (14.77)	6 (10.34)	1 (6.67)	2 (20.00)	1 (9.09)	
I have never used this treatment	141 (77.47)	67 (76.14)	46 (79.31)	11 (73.33)	8 (80.00)	9 (81.82)	
Teriflunomide (Aubagio), n (%)							0.240
I am currently using this treatment	14 (7.69)	3 (3.41)	8 (13.79)	1 (6.67)	1 (10.00)	1 (9.09)	
I have used this treatment in the past	20 (10.99)	12 (13.64)	5 (8.62)		1 (10.00)	2 (18.18)	
I have never used this treatment	148 (81.32)	73 (82.95)	45 (77.59)	14 (93.33)	8 (80.00)	8 (72.73)	
Cladribine (Mavenclad), n (%)							0.115
I am currently using this treatment	1 (0.55)					1 (9.09)	
I have never used this treatment	181 (99.45)	88 (100.00)	58 (100.00)	15 (100.00)	10 (100.00)	10 (90.91)	

Fingolimod (Gilenya), n (%)							0.554
I am currently using this treatment	19 (10.44)	9 (10.23)	7 (12.07)	1 (6.67)		2 (18.18)	
I have used this treatment in the past	13 (7.14)	5 (5.68)	5 (8.62)		1 (10.00)	2 (18.18)	
I have never used this treatment	150 (82.42)	74 (84.09)	46 (79.31)	14 (93.33)	9 (90.00)	7 (63.64)	
INFUSION							
Alemtuzumab (Lemtrada), n (%)							0.737
I am currently using this treatment	6 (3.30)	4 (4.55)	1 (1.72)	1 (6.67)			
I have never used this treatment	176 (96.70)	84 (95.45)	57 (98.28)	14 (93.33)	10 (100.00)	11 (100.00)	
Natalizumab (Tysabri), n (%)							0.265
I am currently using this treatment	8 (4.40)	2 (2.27)	3 (5.17)	1 (6.67)	1 (10.00)	1 (9.09)	
I have used this treatment in the past	23 (12.64)	11 (12.50)	10 (17.24)			2 (18.18)	
I have never used this treatment	151 (82.97)	75 (85.23)	45 (77.59)	14 (93.33)	9 (90.00)	8 (72.73)	
Ocrelizumab (Ocrevus), n (%)							0.003
I am currently using this treatment	39 (21.43)	29 (32.95)	5 (8.62)		3 (30.00)	2 (18.18)	
I have used this treatment in the past	3 (1.65)	1 (1.14)	2 (3.45)				
I have never used this treatment	140 (76.92)	58 (65.91)	51 (87.93)	15 (100.00)	7 (70.00)	9 (81.82)	

DMF: dimethyl fumarate, GA: glatiramer acetate, INF-β: Interferon beta, PegINF- β: peginterferon beta. [a]: Fisher's exact test.

Appendix A2 Spearman correlation coefficient of the total study population

	EDSS	P-value
Mobility	0.83	<0.001
Self-care	0.68	<0.001
Usual activities	0.73	<0.001
Pain / discomfort	0.46	<0.001
Anxiety / depression	0.06	0.55

EDSS: Expanded disability status scale.

Appendix A3 Predictors of EQ-5D-5L dimensions (univariate regression analysis) of the total study population

	Mobility					Self-care					Usual activities				
	No	Slight	Moderate	Severe	Unable to	No	Slight	Moderate	Severe	Unable to	No	Slight	Moderate	Severe	Unable to
Age		0.046**	0.081***	0.148***	0.148**		0.039**	0.033	0.068	0.163**		0.017	0.060***	0.072***	-0.042
Age at diagnosis		0.017	0.050**	0.139***	-0.021		0.048**	0.049**	0.057	0.048		0.003	0.026	0.058**	-0.023
Time since diagnosis		0.054*	0.060**	0.013	0.184***		-0.015	-0.033	0.017	0.108*		0.030	0.066*	0.029	-0.054
Gender (male 0, female 1)		-0.230	-1.066**	-0.823	-1.922*		-0.065	-1.319**	-1.520	13.422		1.245	2.184*	1.353	12.527
Marital status															
Single															
Partnered		-1.098*	-1.098*	-2.890**	-1.791		-0.827	-0.174	-15.293	14.316		-0.074	0.099	-0.806	-15.165
Married		-0.278	-0.532	-0.096	-1.993		-0.134	-0.511	-1.792	14.267		-0.470	0.289	-0.677	-15.161
Divorced		-0.406	0.325	0.693	-12.290		0.966	-14.555	1.253	-0.169		-0.241	15.575	14.285	15.671
Widowed		14.066	-0.580	-0.483	-1.365		16.434	-0.331	-1.025	14.054		15.699	0.261	-0.506	-1.317
Educational level															
Primary education															
Secondary education		16.301	17.674	17.839	18.721		15.171	15.813	17.016	0.735		18.911	19.161	18.301	20.498
Vocational/technical education		17.705	17.615	17.685	3.169		14.908	14.857	0.761	14.556		18.976	19.102	19.177	18.889
University		17.286	17.089	17.072	17.586		14.141	13.866	14.377	14.665		18.036	17.830	17.791	17.503
Other		2.967	18.549	17.839	2.967		15.681	16.323	1.169	1.169		5.072	18.314	18.995	5.072
Type of MS															
CIS / RRMS															
PPMS		0.045[I]	17.173[I]	19.491[I]	19.571[a]		2.349***	3.305***	4.691***	18.701		0.121[I]	16.365[I]	18.082[a]	18.593[a]
SPMS		13.445[I]	14.926[I]	15.335[I]	17.207[a]		1.587***	1.108	2.900**	16.909		15.352[I]	15.311[I]	15.797[a]	17.406[a]
Country of residence															
United Kingdom															
France		-1.658	-2.064*	-2.708**	14.615		-1.259*	-2.685***	-17.599	15.501		-0.318	-1.181	-2.110	-16.481
The Netherlands		-0.588	-1.133	-1.484	14.951		-0.645	-1.427**	-1.204	16.067		-0.051	-0.718	-0.510	-1.608
Spain		-2.890*	-2.484*	-19.033	-2.439		-1.974	-17.899	-17.899	-0.511		-0.405	-2.484*	-2.197	-17.118
Elsewhere		-1.099	-2.079	-18.230	-1.636		-1.281	-17.755	-17.755	-0.366		-0.693	-1.791	-2.197	-16.899
EDSS levels															
EDSS <= 2.5															
EDSS 3 – 5.5		2.351***	4.025***	18.380	19.262		2.447***	1.841	16.057	0.620		16.477	17.681	18.086	33.342
EDSS >= 6		0.803	19.739	36.818	37.124		4.344***	4.586***	19.053	18.935		15.910	18.523	21.183	35.666
Unknown/missing		1.192**	2.108***	17.443	1.482		1.732**	1.984*	0.472	15.389		0.824	1.801***	2.890**	1.526

Current line of treatment															
Treatment naive															
1st-line DMT		1.157	0.658	-1.952 8*	-14.926 [a]		-1.567	-1.750	-17.561[a]	-0.054 [a]		1.609	-0.134	-1.569*	-14.494[a]
2nd-line DMT		2.088*	1.647	-0.638	-0.956		-0.792	-0.811	-17.281[a]	14.681[a]		1.852	0.811	-0.471	-0.287[a]
Treatment experience but currently no DMT		1.860	1.368	-0.807	0.356		-0.734	-1.204	-2.303*	16.185 [a]		1.280	0.531	-0.512	-14.115[a]
**** p<0.01, ** p<0.05, * p<0.1*															

CIS: clinically isolated syndrome, DMT: disease modifying therapy, EDSS: Expanded Disability Status Scale, PPMS: primary progressive multiple sclerosis, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis. [a]: due to small sample size the model was not able to converge (very large standard errors).

Appendix A3 (continued). Predictors of EQ-5D-5L dimensions (univariate regression analysis) of the total study population

	Pain / discomfort					Anxiety / depression					Health utility Univariate [a]	Health utility Multivariate [a]	Health utility Univariate [b]	Health utility Multivariate [b]
	No	Slight	Moderate	Severe	Unable to	No	Slight	Moderate	Severe	Unable to				
Age		0.033	0.076***	0.069**	0.021		-0.005	-0.005	-0.026	0.034	-0.006***		-0.005***	
Age at diagnosis		0.022	0.059**	0.042	0.060		-0.009	0.007	-0.006	0.052	-0.007**		-0.005***	
Time since diagnosis		0.024	0.034	0.049	-0.194		0.005	-0.023	-0.043	-0.039	-0.000		-0.001	
Gender (male 0, female 1)		-0.111	0.357	-0.154	-0.154		-0.035	1.030*	0.385	13.510	0.055		0.020	
Marital status														
Single													0.158***	
Partnered		-0.762	-0.734	-1.609	-0.916		0.270	0.328	-0.876	-15.261	0.119*		0.106**	0.109**
Married		-0.028	0.182	-0.613	-14.691		0.613	0.328	-0.588	-1.568	0.084		-0.037	0.103**
Divorced		-1.098	-0.916	0.695	-16.064		-0.847	-0.693	-15.349	-15.984	-0.070		0.252	
Widowed		-0.267	15.699	-0.622	-1.216		-15.295	-15.441	-16.219	-16.855	0.171			
Educational level														
Primary education														
Secondary education		0.267	-14.397	1.315	-12.494		-16.088	0.013	-0.307	-12.888	-0.296		-0.289	
Vocational/technical education		0.002	-15.601	0.399	0.706		-16.183	-0.392	-0.066	-0.277	-0.223		-0.236	
University		-0.078	-15.224	-0.647	-0.863		-15.583	0.196	0.008	0.356	-0.119		-0.165	
Other		13.410	-1.071	0.000	0.000		-14.701	1.400	1.484	-12.050	-0.160		-0.258	
Type of MS														
CIS / RRMS														
PPMS		0.634	1.160	1.561	3.219**		-0.653	0.098	1.492**	1.674	-0.387***	-0.275***	-0.394***	-0.226***
SPMS		0.857	1.314	1.560	-10.382		0.782	0.792	-12.491	-12.434[c]	-0.143**		-0.136**	

									[c]					
Country of residence														
United Kingdom														
France		0.140	-0.356	-0.762	-0.916		0.811	0.251	1.232	15.675	0.281***	0.126***	0.096	
The Netherlands		-0.923	-1.406	-1.041	-2.833		-0.521	-0.827	-0.134	-0.330	0.098		0.092	
Spain		-1.386	-1.504	-15.979	-16.861		0.118	-0.288	0.405	0.013	0.293***		0.250**	
Elsewhere		0.223	-0.405	-1.098	-15.480		0.405	0.917	-13.625	0.064	0.195*		0.189*	
EDSS levels														
EDSS <= 2.5														
EDSS 3 -5.5		1.099	2.190**	2.110**	14.912		-0.351	-0.100	-1.044	-13.796	-0.161***	-0.129***	-0.157***	-0.126**
EDSS >= 6		0.916	2.516**	3.314***	14.911		0.236	0.528	1.376	-13.346	-0.485***	-0.383***	-0.458***	-0.376***
Unknown / missing		-0.123	1.155**	0.644	12.346		-0.332	0.542	0.524	0.236	-0.151***	-0.113***	-0.138***	-0.130***
Current line of treatment														
Treatment naive														
1st-line DMT		-0.223	-0.270	-1.992*	-1.705		1.600*	1.482*	0.788	-13.305[c]	0.259 ***		0.204***	
2nd-line DMT		0.145	-0.022	-0.251	-0.811		1.300	0.943	1.076	-1.004	0.115		0.100	
Treatment experience but currently no DMT		-0.328	-0.041	-0.223	-14.253[c]		1.369	0.675	1.145	-0.242	0.127 *		0.080	

CIS: clinically isolated syndrome, DMT: disease modifying therapy, EDSS: Expanded Disability Status Scale, PPMS: primary progressive multiple sclerosis, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis. [a] Regression with the utility calculated using the country-specific tariffs; [b] Regression was re-run with the utility calculated using only the Dutch tariffs; [c]: due to small sample size the model was not able to converge (very large standard errors).

Appendix A4 Predictors of MSQOL-54 scales (univariate regression analysis) of the total study population

	PH	**HP**	**E**	**RLPP**	**P**	**SFMF**	**HD**	**PHCS** Univariate	**PHCS** Multivariate
Age	-1.192***	-0.005	0.116	-0.156	-0.351*	-0.305	0.086	-0.257**	
	(0.198)	(0.160)	(0.140)	(0.264)	(0.180)	(0.191)	(0.174)	(0.120)	
Age at diagnosis	-0.905***	0.105	0.104	-0.017	-0.230	-0.067	-0.084	-0.159	
	(0.210)	(0.162)	(0.143)	(0.269)	(0.184)	(0.196)	(0.177)	(0.124)	
Time since diagnosis	-0.577**	-0.194	0.028	-0.254	-0.234	-0.437*	0.304	-0.190	
	(0.289)	(0.215)	(0.190)	(0.356)	(0.245)	(0.257)	(0.234)	(0.163)	
Gender (male 0, female 1)	9.487*	-5.885	-1.777	5.119	-4.604	-0.794	-0.395	0.482	
	(5.482)	(4.062)	(3.601)	(6.767)	(4.635)	(4.934)	(4.428)	(3.098)	
Marital status									
Single									
Partnered	16.484**	-0.724	-2.249	-3.671	6.435	6.030	7.579	3.770	
	(6.818)	(5.111)	(4.512)	(8.439)	(5.811)	(6.235)	(5.558)	(3.923)	
Married	3.771	6.901	2.527	9.549	8.067	3.008	10.937**	5.372	
	(5.866)	(4.398)	(3.882)	(7.262)	(5.000)	(5.379)	(4.782)	(3.384)	
Divorced	-16.942	4.435	-8.439	-9.226	-10.747	1.672	13.056	-4.081	
	(12.399)	(9.295)	(8.205)	(15.349)	(10.568)	(11.279)	(10.108)	(7.097)	
Widowed	-14.799	-10.208	16.704	-27.083	-5.509	37.379	-1.944	-3.549	
	(30.431)	(22.812)	(20.137)	(37.670)	(25.937)	(27.629)	(24.808)	(17.383)	
Educational level									
Primary education									
Secondary education	-69.872**	-27.308	-34.154*	-78.846**	-16.667	-42.960	-30.000	-38.651**	-9.409**
	(30.548)	(23.450)	(20.378)	(37.970)	(26.694)	(27.865)	(25.689)	(17.450)	(4.490)
Vocational/technical education	-50.265*	-26.051	-39.806**	-78.109**	-14.005	-21.896	-30.597	-33.782**	-6.424**
	(29.656)	(22.765)	(19.783)	(36.861)	(25.914)	(27.051)	(24.938)	(16.940)	(2.471)
University	-38.257	-21.478	-33.719*	-63.070*	-7.579	-26.601	-30.088	-27.890	
	(29.592)	(22.716)	(19.740)	(36.781)	(25.858)	(26.994)	(24.884)	(16.905)	
Other	-50.833	-28.889	-43.333**	-58.333	-16.944	-23.613	-28.333	-32.622*	
	(31.796)	(24.408)	(21.210)	(39.521)	(27.784)	(29.003)	(26.738)	(18.163)	
Type of MS									

CIS / RRMS									
PPMS	-44.048***	-13.521**	-9.258*	-25.467***	-18.341***	-21.186***	-27.839***	-21.055***	-14.799***
	(6.858)	(5.712)	(5.062)	(9.401)	(6.460)	(6.983)	(5.975)	(4.219)	(4.043)
SPMS	-32.284***	-5.580	2.036	-12.232	-7.753	-8.781	0.102	-9.204**	
	(6.858)	(5.712)	(5.062)	(9.401)	(6.460)	(6.795)	(5.975)	(4.105)	
Country of residence									
United Kingdom									
France	35.110***	1.406	2.941	18.391*	9.272	11.086	-2.655	10.251**	
	(8.347)	(6.455)	(5.607)	(10.607)	(7.410)	(7.901)	(7.080)	(4.968)	
The Netherlands	20.805**	3.891	11.488**	9.375	14.331**	20.771***	3.326	10.174**	5.364**
	(8.049)	(6.225)	(5.408)	(10.228)	(7.146)	(7.635)	(6.828)	(4.800)	(2.445)
Spain	43.259***	19.639**	16.733**	43.333***	18.111*	27.266**	16.500*	23.758***	11.074***
	(11.763)	(9.098)	(7.903)	(14.948)	(10.444)	(10.986)	(9.979)	(6.907)	(5.002)
Elsewhere	41.259***	14.222	16.533**	21.970	17.172*	21.819**	4.727	18.075***	
	(11.438)	(8.846)	(7.684)	(14.535)	(10.155)	(10.691)	(9.703)	(6.722)	
EDSS levels									
EDSS <= 2.5									
EDSS 3 – 5.5	-26.887***	-11.319**	-8.875**	-22.460***	-9.201	-8.020	-4.794	-12.436***	-11.320***
	(5.574)	(4.833)	(4.396)	(8.171)	(5.635)	(5.929)	(5.465)	(3.482)	(3.419)
EDSS >= 6	-60.314***	-22.660***	-13.150***	-29.915***	-20.540***	-23.782***	-16.735***	-25.362***	-21.194***
	(6.092)	(5.282)	(4.805)	(8.931)	(6.159)	(6.562)	(5.973)	(3.854)	(3.997)
Unknown / missing	-20.418***	-15.286***	-9.198**	-18.823***	-2.682	-12.847**	-7.077	-11.534***	-10.677***
	(4.652)	(4.033)	(3.669)	(6.819)	(4.703)	(4.949)	(4.561)	(2.906)	(2.851)
Current line of treatment									
Treatment naive									
1st-line DMT	29.700***	2.793	2.744	20.250**	12.574*	6.233	8.611	10.778**	
	(8.072)	(6.221)	(5.517)	(10.234)	(7.053)	(7.687)	(6.806)	(4.785)	
2nd-line DMT	11.634	-3.869	1.165	8.508	7.048	9.643	7.127	4.477	
	(7.882)	(6.074)	(5.387)	(9.993)	(6.886)	(7.514)	(6.646)	(4.677)	
Treatment experienced but currently no DMT	11.422	1.164	2.235	9.559	2.892	6.098	7.549	4.857	
	(8.694)	(6.700)	(5.942)	(11.022)	(7.596)	(8.252)	(7.331)	(5.137)	
**** p<0.01, ** p<0.05, * p<0.1 Standard errors are in parenthesis*									

CIS: clinically isolated syndrome, DMT: disease modifying therapy, E: energy / fatigue, EDSS: Expanded Disability Status Scale, HD: health distress, HP: health perception, P: pain, PF: physical function, PHCS: physical health composite score, PPMS: primary progressive multiple sclerosis, RLP: role limitation physical, RRMS: relapsing-remitting multiple sclerosis, SFMF: sexual function male and female combined, SPMS: secondary progressive multiple sclerosis.

Appendix A4 (continued). Predictors of MSQOL-54 scales (univariate regression analysis) of the total study population

	HD	**OQOL**	**EWB**	**RLEP**	**CF**	**MHCS** Univariate	**MHCS** Multivariate
Age	0.086	-0.152	0.292**	0.148	0.356**	0.149	
	(0.174)	(0.134)	(0.147)	(0.312)	(0.174)	(0.154)	
Age at diagnosis	-0.084	-0.295**	0.166	-0.072	0.245	-0.010	
	(0.177)	(0.135)	(0.151)	(0.316)	(0.178)	(0.156)	
Time since diagnosis	0.304	0.244	0.240	0.390	0.217	0.282	
	(0.234)	(0.181)	(0.200)	(0.416)	(0.237)	(0.205)	
Gender (male 0, female 1)	-0.395	2.534	-7.209*	-8.626	-0.139	-3.742	
	(4.428)	(3.457)	(3.768)	(7.857)	(4.517)	(3.883)	
Marital status							
Single							
Partnered	7.579	7.036	4.337	11.485	2.791	6.816	
	(5.558)	(4.334)	(4.784)	(10.071)	(5.663)	(4.958)	
Married	10.937**	6.063	5.726	10.989	6.082	7.889*	
	(4.782)	(3.730)	(4.116)	(8.712)	(4.873)	(4.289)	
Divorced	13.056	5.911	11.885	4.342	13.386	9.444	
	(10.108)	(7.883)	(8.701)	(18.118)	(10.299)	(8.921)	
Widowed	-1.944	6.618	14.028	51.961	-5.185	16.736	
	(24.808)	(19.347)	(21.353)	(44.290)	(25.277)	(21.807)	
Educational level							
Primary education							
Secondary education	-30.000	-12.192	-23.077	-38.462	-5.000	-23.068	
	(25.689)	(19.889)	(21.752)	(45.404)	(25.866)	(22.460)	
Vocational/technical education	-30.597	-11.283	-22.627	-45.274	-9.080	-25.104	
	(24.938)	(19.308)	(21.116)	(44.078)	(25.111)	(21.803)	
University	-30.088	-8.393	-27.537	-43.369	-2.719	-24.458	
	(24.884)	(19.266)	(21.070)	(43.987)	(25.056)	(21.759)	
Other	-28.333	-14.467	-34.000	-27.778	-10.833	-24.722	
	(26.738)	(20.701)	(22.640)	(47.258)	(26.923)	(23.377)	
Type of MS							
CIS / RRMS							
PPMS	-27.839***	-20.153***	-13.220**	-22.012**	-2.471	-17.066***	-17.815***
	(5.975)	(4.665)	(5.300)	(10.971)	(6.361)	(5.343)	(5.326)
SPMS	0.102	-0.003	4.545	19.165*	8.706	7.183	

	(5.975)	(4.665)	(5.300)	(10.971)	(6.361)	(5.343)	
Country of residence							
United Kingdom							
France	-2.655	7.724	-6.638	-5.380	-6.822	-3.051	
	(7.080)	(5.451)	(5.837)	(12.566)	(7.233)	(6.137)	
The Netherlands	3.326	12.868**	8.091	9.885	-1.807	7.168	
	(6.828)	(5.257)	(5.629)	(12.106)	(6.975)	(5.912)	
Spain	16.500*	15.975**	6.000	16.667	0.500	11.000	
	(9.979)	(7.683)	(8.227)	(17.678)	(10.193)	(8.633)	
Elsewhere	4.727	13.176*	6.636	-4.848	-7.545	2.663	
	(9.703)	(7.470)	(7.999)	(17.189)	(9.912)	(8.395)	
EDSS levels							
EDSS <= 2.5							
EDSS 3 – 5.5	-4.794	-5.191	3.327	3.961	-8.878	-1.415	
	(5.465)	(4.149)	(4.730)	(9.875)	(5.560)	(4.847)	
EDSS >= 6	-16.735***	-17.857***	-4.044	-0.874	-3.041	-7.789	
	(5.973)	(4.535)	(5.170)	(10.785)	(6.077)	(5.294)	
Unknown / missing	-7.077	-5.545	-3.781	-8.293	-10.202**	-7.121*	
	(4.561)	(3.463)	(3.947)	(8.279)	(4.640)	(4.064)	
Current line of treatment							
Treatment naive							
1st-line DMT	8.611	8.965*	-3.940	-0.068	0.328	1.709	
	(6.806)	(5.226)	(5.831)	(12.062)	(6.845)	(5.970)	
2nd-line DMT	7.127	4.424	-3.853	6.683	-7.185	1.259	
	(6.646)	(5.103)	(5.693)	(11.809)	(6.684)	(5.844)	
Treatment experienced but currently no DMT	7.549	9.750*	-1.706	7.843	-5.000	3.450	
	(7.331)	(5.628)	(6.280)	(12.991)	(7.372)	(6.429)	
**** p<0.01, ** p<0.05, * p<0.1 Standard errors are in parenthesis*							

CF: cognitive function, CIS: clinically isolated syndrome; DMT: disease modifying therapy, EDSS: Expanded Disability Status Scale, EWB: emotional well-being, HD: health distress, MHCS: mental health composite score, OQOL: overall quality of life, PPMS: primary progressive multiple sclerosis, RLE: role limitation emotional, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis.

PART II

ARE WE ABLE TO QUANTIFY THE PATIENT NEEDS IN A QUALITATIVE AND QUANTITATIVE MANNER?

4

INNOVATIVE MEDICAL TECHNOLOGY AND THE TREATMENT DECISION-MAKING PROCESS IN MULTIPLE SCLEROSIS: A FOCUS GROUP STUDY TO EXAMINE PATIENT PREFERENCES

L.A. Visser, M. de Mul, W.K. Redekop. Patient Preferences and Adherence (2021).

ABSTRACT

Background: Disease-modifying therapies are given to people with multiple sclerosis (MS) to reduce disease progression and relapse frequency. Current modes of administration include oral, injectable and infusion therapy and the treatment decision-making process is complex. A novel mode of treatment administration, an implantable device, is currently under development, yet patient attitudes about the device are unknown. The aim of this study was 1) to understand the treatment decision-making process from the patient perspective and 2) to explore the possible acceptance of an implant to treat MS.

Methods: Focus groups with people with MS were conducted in the Netherlands. Three topics were addressed: the treatment decision-making process, the current treatment landscape, and attitudes about the implantable device. All focus groups were recorded and transcribed and data was analyzed by raw data coding and creating themes. An online survey was conducted in the Netherlands to quantify interest in an implant.

Results: Two focus group sessions were held (n=16 participants) and n=93 persons filled out the survey. The main theme that emerged was the constant uncertainty persons with MS face throughout their disease course and during treatment decisions (when to start, stop, continue or switch treatment). Patients were generally positive towards the implant but felt that efficacy and safety should be guaranteed.

Conclusion: People with MS want some form of control over their disease and treatment course. New medical technologies, such as an implant, may enhance the treatment landscape and with caution we postulate that it may be accepted by patients as a new mode of administration, though further research is needed. For medical technologies to be successful, patients should be engaged early on in the design process.

INTRODUCTION

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system affecting 700,000 persons in Europe. (161) Symptoms of MS include unilateral optic neuritis, asymmetrically reduced strength in the extremities and bowl and bladder dysfunction. MS is characterized by periods of neurological dysfunction, called a relapse, which the patient may partially or fully recover from, alternated with periods of remission. (51)

Once diagnosed, people with MS can be treated with various disease modifying treatments (DMTs) to reduce the frequency of relapses and disease progression. DMTs differ in efficacy, safety and mode of administration. (9,162) Treatments currently available on the market can either be taken at home, such as oral treatment and injections, or given in a hospital setting, such as infusion therapies. A new mode of administration is currently under development by the Optogenerapy consortium through a European Horizon 2020 funded project. Specifically, the consortium has been developing an optogenetics implant that will allow for the controlled release of beta interferon protein (INFβ) delivery into the body. (27,163) However, it is yet unknown whether people with MS feel the need for a new mode of administration and what drives their treatment decision-making process.

The aim of this study was two-fold: to understand the decision-making process in current MS care from a patient perspective and to explore the possible acceptance of implant therapy for MS.

MATERIALS AND METHODS

Two separate qualitative and quantitative methods for data collection were used. Focus group sessions with people with MS were conducted to get a deeper understanding of the treatment decision-making process and acceptability of an implant. A focus group is a method in which less than 10 people converse with each other, and share views and opinions about the questions raised by the focus group researcher. (164) The Consolidated Criteria for Reporting Qualitative research checklist was used to structure this manuscript. (165)

To quantify the possible acceptance of implant therapy, a European health-related quality of life (HRQOL) survey was performed between June and October 2019. The results and methodology are reported elsewhere. (166) In addition to examining the HRQOL, patients were asked whether they would be interested in the Optogenerapy implant and to elaborate why, or why not, they would be interested (see Appendix 1). The results from the Dutch sample are included in the current paper.

Patient recruitment and ethics

The goal was to have a minimum of two focus groups with at least five persons with MS per group to achieve data saturation. Participants had to be older than 18 years of age, and no restrictions were made regarding type of MS and whether participants were currently using a DMT or not. We were primarily interested in the treatment decision-making process and therefore we did not exclude patients that were not eligible for INFβ treatment (such as patients with more severe MS (10)). Participants were given a gift card worth €10 as a mean of thanks for participating.

Participants were recruited by contacting local MS patient organizations in the Netherlands and emailing them with the question whether it was possible to give a brief presentation about the Optogenerapy project followed by a focus group session. Ten local MS patient organizations spread out over the Netherlands were contacted. The local organizations reached out to their members, and provided us with a list of interested members, which we checked for eligibility. Two organizations reacted positively to the request, two organizations declined participation and six locations did not respond to the email. Medical ethical approval was obtained for the focus groups by the Medical Research Ethics Committee of the Erasmus Medical Center (MEC-2019-0248). The study was conducted in accordance with the Declaration of Helsinki.

Study design

The focus group sessions were held in September and October 2019. One researcher was present at each session (LV) and is trained in conducting interviews. Before the start of the focus group session, participants had to give written informed consent and their permission for the session to be audio recorded. Participants completed a short self-reported questionnaire on patient demographics at the start of the session (Appendix 2). A structured interview guide was followed (Appendix 3).

As the researcher had no prior relationships with the participants, the focus group session started with a 15-minute introduction of the Optogenerapy project and implant (Appendix 4). (27,163) The focus group itself consisted of an introduction, explaining the 'rules' of the focus group, and three main topics: the treatment decision-making process, the current treatment landscape, and the Optogenerapy implant.

Data analysis

Audio recordings and notes made during the meeting were fully transcribed. The transcripts of the focus groups were not returned to the participants for comments. Three authors (LV, MM, KR) independently used the systematic process of inductively coding the raw data and identifying statements to interpret the lived experience. This was followed by creating themes to cluster the meaning of the statement, and these themes were discussed until consensus was reached. Finally, the themes are described using textual descriptions. (167) The qualitative data analysis was performed in Atlas.ti 8 software.

The open text fields of the online survey were translated to English by the first author (LV), and checked by a native speaker and co-author of this paper (WKR). The statements were coded thematically and grouped into topics, and these topics were discussed until consensus was reached.

RESULTS

Patient demographics

Two focus groups were held with a total of 16 participants (focus group A: n=10, focus group B: n=6). Both focus group sessions had a duration of 1 hour. They were held at a local community center where the members of the patient organization meet every month. All

members with MS gave permission to participate in the focus group session; in both groups a spouse without MS was present during the session but did not participate in the discussion.

A total of 134 Dutch patients started the survey. Patients were dropped from the analysis if they did not complete the survey (n=17), did not give informed consent (n=13), did not live in the Netherlands (n=9), and stated that their age of diagnosis was older than their current age (n=2). This left 93 patients for analysis.

Patient demographics can be found in Table 1. The mean age of the participants of the focus group sessions was higher than the respondents in the survey (61 vs 44 years); their average age at diagnosis was also older (42 vs 35 years). The diagnosis and disability status were self-reported (and not verified by a neurologist). The majority of the patients were female (81% and 70%), had RRMS (56% and 72%), and were married (75% and 47%). The majority of the focus group participants were currently not taking DMT (56%); whereas half of the survey respondents were taking second-line DMT (50%).

Table 1 Patient demographics

	Total (n=16)	**Online survey (n=93)**
Age, mean (range)	61 (48 – 82)	44 (23 – 70)
Age at diagnose, mean (range)	42 (29-70)	35 (15 – 64)
Gender, n (%)[a]		
Male	3 (19)	22 (24)
Female	13 (81)	70 (75)
MS Type[b]		
RRMS	9 (56)	72 (77)
PPMS	2 (13)	11 (12)
SPMS	4 (25)	9 (10)
Disease severity, n (%)[c]		
Mild	1 (6)	19 (20)
Moderate	8 (50)	20 (22)
Severe	4 (25)	4 (4)
Unknown	3 (19)	33 (18)
Treatment, n (%)		
Treatment naïve	4 (25)	10 (11)
Treatment experienced, but not currently on DMT[d]	9 (56)	20 (22)
On 1st line DMT	2 (13)	17 (18)
On 2nd line DMT	1 (6)	46 (50)
Marital status, n (%)		
Single		19 (20)
Partnered	1 (6)	23 (25)
Married	12 (75)	44 (47)
Divorced	1 (6)	5 (5)
Widowed	2 (13)	2 (2)
Education, n (%)		
Primary/ secondary education	7 (44)	10 (11)
Vocational/ technical education	7 (44)	44 (47)
University	2 (13)	39 (42)

MS: multiple sclerosis; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis. [a]The online survey also provided the answer category: prefer not to say (n=1), [b]The online survey also provided the answer category: clinically isolated syndrome (n=1), [c]The online survey had n=17 (18%) missing, [d]In the focus groups the number of past disease-modifying therapies (DMT) used ranged from 1-4.

Focus group sessions

Three main themes (uncertainty vs control, the treatment decision-making process, and the implantable device) emerged from the analysis of the focus group sessions (contribution of codes to the finalized themes can be found in Table 2). Quotes are followed by indicating the gender (F: female, M: male) and age (in years) of the participant.

Table 2 Codes used for the inductive analysis to the finalized themes

Theme	Contributing codes
Uncertainty vs. control	- Adverse events - Body failing to cooperate - Causes of MS unknown - Efficacy of DMT unknown and the effect of DMT on the body - Frustration that new research and development of DMTs is focussed on reducing disease progression - Uncertainty of disease progression
The decision-making process	- Reasons for initiation of DMT (the need to understand MS before starting treatment; trade-offs regarding treatment choice: efficacy, safety profile, mode of administration) - Reasons for continuation of the DMT (hope; at ease with current DMT) - Reasons for discontinuation of the DMT (adverse events; doubts about efficacy; disease progression) - Shared decision-making with health care practitioner
The implantable device	- Concerns about the implant (efficacy; safety profile) - Confrontation of being sick - Reasons to opt for the implant (or not)

DMT: disease-modifying therapy.

Uncertainty vs control

The underlying theme across all phases of the disease and during the treatment decision-making process is uncertainty. Receiving the diagnosis "multiple sclerosis" may be perceived as a relief after a period of symptoms without any diagnosis. However, this results in the uncertainty associated with that diagnosis and not knowing what MS entails. Persons with MS are in the dark about how their disease will progress over time and the impact it will have on their lives.

"I am still very much in the denial phase, I don't want it. In my head I can still do so much, while when actually doing something I quickly have to stop because I just can't do it anymore. So I am really still in that phase, yes: I still want to try. I still want to do so much." (F, 48).

The uncertainty associated with the treatment decision-making process is evident during multiple phases of the disease course: at the start (concerns about if and when one should start taking a DMT), during the treatment course (concerns about the efficacy of the treatment), and when ceasing treatment (concerns about how the MS will progress without treatment). Furthermore, the treatment decision-making process is complicated because of the many DMTs available and having to choose the DMT that fits best into the life of the patient. All of these doubts and

factors may have an impact on whether a person with MS is willing to start and continue with the treatment regimen.

"It just gets you thinking, what are you doing? If you continue injecting and you do not know whether it will work or not. I just thought 'I will never know if I do not take it, or do take it, what the difference will be, because I just do not know how I do it by myself [without DMT]'." (F, 71)

The uncertainty makes the participants want to have some form of control over their disease. A large majority of the focus group participants, at some point during their disease course, opted to start taking one or more DMTs. By taking control over the disease some of the uncertainty is reduced thereby motivating the participants to continue therapy. As such, they show resilience against MS because they do not want to give in to the disease.

"This month I started Natalizumab. Before that, I use Tecfidera, Copaxone and Fingolimod. All three didn't achieve the miracles that I had wished for. And now with Tysabri, I am hoping for a future with reduced disease progression." (F, 55)

The decision-making process

When confronted with the diagnosis and being encouraged by a health care professional (HCP; physician or MS nurse) to start a DMT, patients feel overwhelmed and may choose not to start a DMT right away. The decision to start taking the DMT is made together with the HCP, whereas the choice to switch to another DMT or stop a DMT is made primarily by the patient or together with the HCP when DMT is no longer effective in preventing progression. During the shift from being unexperienced with the disease to being more experienced, the patient feels more empowered to make his/her own decisions.

"*When I had my first appointment with the neurologist, he told me how I should be treated. That was way too fast for me. I didn't even know what MS was. So I told him, I don't want it just yet. First I want to see what my own body does. I mean, it doesn't have be so aggressive. Because, how should I know? Two years later I did start [a DMT]. But then you know what MS is, and I did that for almost two years. But that I am not doing again either." (F, 71)*

The choice of treatment is intertwined with the process of coming to terms with having MS. This is a complicating factor, because the trade-off has to be made between wanting to understand MS and coming to terms with the diagnosis before starting a DMT, or starting a DMT immediately but not knowing how the disease would progress without an intervention. Once diagnosed, the HCP encourages the use of a DMT as soon as possible. As such, the shared decision-making between HCP and patient is important, given the uncertainty the patient feels and the patient not knowing what DMT is best for him/herself. Therefore, the information given by the HCP should be clear regarding the efficacy and other aspects of the treatment.

"When I got MS 4 years ago, the first year I didn't take anything until I had more spots after a relapse. They told me to go to the MS nurse, and there I was given a list with pros and cons and the side effects…so then you choose something with the least side effects. Was that the right choice? I have had the disease for such a short

period, so I can't say anything about the long-term. I mean, what is four years? Of which I have had Tecfidera for two. But hey, they [the HCP] can't say anything about the long-term effects either." (F,48)

The choice for a DMT can be a rational and well-considered process based on weighing the importance of frequency and mode of administration, efficacy and safety. However, other participants mention that it was based on circumstantial information rather than such attributes.

"The reason why I started injecting was because I thought, if the health insurance companies are willing to reimburse such an expensive drug, then it should be proven somewhere that it works. That was my only reason to start injecting. Even though I had heard only negative stories about it, actually." (M, 55)

A mechanism to cope with disease uncertainty is by taking a DMT. It is possible that participants with past treatment experience continue their current line of therapy because of their past experiences. Furthermore, past (negative) experiences (commonly due to side effects) made participants switch. Participants accept their current therapy and are willing to continue if they experience less or no side effects compared to past therapy. Nevertheless, participants are willing to accept a degree of side effects, or an inferior mode of administration, because they find it burdensome to switch again. Still, the core reason for continuing treatment is driven by the hope and fear that doing nothing will cause a more severe disease state.

"I am afraid to stop [with DMT], because now things are going pretty well. I can walk a bit, I can do a bit of this and that. And if I stop and I have a relapse, I am just so very scared for that." (F, 48)

The participants have vast experience with MS (time since diagnosis ranged from 3-51 years) which has allowed them to reflect on the uncertainty that comes with having MS. Doubts regarding the effect DMTs (may) have on the body and not knowing how one's body works with or without DMTs crossed their minds during the decision-making processes. Adverse events and disease progression enhance the concerns of whether the disadvantages of taking a treatment weigh against the potential health benefits. These apprehensions give them the courage to discontinue their treatment. Such a choice, and knowing that discontinuing may worsen their prognosis, shows that suffering from side effects may be worse than not knowing what the future may hold for them. Nevertheless, making that choice and accepting what may come regarding their disease progression is a difficult process to go through. Some participants, however, are reluctant to give up the hope of a 'progression-free' future. Therefore, they may continue the treatment regime or switch to a more efficacious therapy. Notwithstanding, the need for new treatments that will cure rather than delay progression is great, and while the participants might have accepted MS to some degree, the underlying urge to conquer the disease remains.

"I took Rebif for two years. At a certain moment in time it became so painful and the skin became hard. I told myself 'I am no longer going to hurt myself, I am quitting this stuff.' I stopped and thought 'whatever happens, happens but I am done with it'." (F, 71)

"Why do they then have to continuously make more and more and more medications that reduce progression? If they had less side effects, then I would understand. But those side effects remain exactly the same." (M, 49)

The implantable device

A new mode of administration such as the implantable device can be an enhancement to the current treatment landscape. However, the true need is a cure for MS and not a treatment with an efficacy and safety profile comparable to currently available treatments. Nevertheless, the participants were generally positive towards the implant. The implant has the ability to reduce the confrontation of being ill which can be experienced when having to inject treatment. However, not all modes of administration are seen as confrontational, such as taking a pill or a monthly visit to the hospital for infusion therapy.

"I find injecting confrontational. A pill you can just take, as if it's a vitamin. When having MS you are already constantly confronted with it, and this [taking injections] creates even more confrontation." (F, 55)

The implant is a mode of administration that can be given to patients at various stages in their disease course. Participants were willing to opt for the implant if they were suitable for it. However, given the long disease experience of most of the participants, they acknowledged that, in the light of the implant now being developed to release INFβ, perhaps it would be best suited for patients with a mild disease course or relatively newly diagnosed. Nonetheless, some participants mentioned that, if they were eligible for the implant they would choose it. The implant is a way to improve the quality of life. Nevertheless, it has to suit one's preference, since one participant mentioned a fear of implantable devices in the body.

"If you were given the choice between stopping the injections and starting with the implant, then I would choose the latter. I would say, fine, let's do it. Because you can just get up and go on." (F, 54)

"I would choose it, even now, and in 10 years' time also. If I were eligible." (F, 62)

Given the yet unclear efficacy rates and side effect profile participants want certainty of those outcomes before starting such a mode of administration.

"I would only allow it if you did not get sick from it. If you do not notice it... But as long as such information cannot be given, I am going to wait until others have tried it." (M, 55)

In line with all the concerns raised during the decision-making process, patients want certainty on how this mode of administration can benefit them in the midst of the uncertainty that they already face daily.

Online survey results

Overall, three-quarters of the patients stated that they were (somewhat) interested in using the device (yes: n=19 (20.4%); maybe: n=49 (52.7%); no: n=25 (26.9%)). Amongst persons more recently diagnosed (≤6 years; n=46/93 (49%), calculated by subtracting current age by age at diagnosis), most were somewhat interested in using the device (yes: n=14/19 (74%); maybe: n=29/49 (59%); no: n=3/25 (12%)). Most persons with 7 to 39 years since time of diagnosis (n=47/93 (51%)) were not interested in the device. Some patients gave more than one reason why they would or would not be interested in the device.

Five main topics were identified that played a role in the interest in the device: the process of administering treatment, (no) need for the implant, efficacy-related reasons, side effects, and bodily integrity (Table 3). Most quotes were related to the process of administering treatment, such as the ease of use of the implant, and the effect on treatment adherence. The (lack of) need for the implant was driven by the current DMT taken by the survey respondents. The respondents mention that the efficacy of INFβ is insufficient, and that is a reason why they would not choose the implant. Also, more evidence regarding the implant results is needed before persons would choose the implant. The side effect profile of INFβ impacts the interest for the device as well. Respondents expect fewer side effects from the implant, but others also explicitly state that they would not choose the implant because of the known side effects of INFβ. The respondents that would perhaps choose the implant are most concerned about their bodily integrity.

Table 3 Topics and related quotes that play a role in the interest in the Optogenerapy implant

Topic	Interest in device	Example quotes
The process of administering treatment (n=30)	Yes (n=13)	'Ease of use' 'I would not forget taking my medication' 'No more daily confrontation with MS'
	Maybe (n=16)	'Not easy to stop the treatment when experiencing side effects' 'I find it a bit scary' 'I think the implant can have positive effects on mental well-being'
	No (n=1)	'I feel like all the medications I have used for MS have only made the MS worse'
Need or no need (n=25)	Yes (n=5)	'Good alternative to current medication because of difficulty injecting and swallowing' 'Would have chosen the device in the past (when still injecting), now switched to infusion therapy'
	Maybe (n=11)	'I get the same results by smoking a joint' 'Currently I have a treatment that I don't have to administer myself'
	No (n=9)	'No current DMT use; however, interested if DMT use was needed' 'Enough implantable devices in the body already'
Efficacy (n=23) **INFβ is not the correct DMT for the patients:**		
	Yes (n=0)	
	Maybe (n=3)	'I have primary progressive MS, INFβ doesn't work for me' 'INFβ is not the right medication for me'
	No (n=7)	'I am not against the implant, but the medication that is given' 'I have secondary progressive MS, INFβ doesn't work for me'
Efficacy of INFβ is insufficient:		
	Yes (n=0)	
	Maybe (n=3)	'It depends on the percentage of reducing the disease progression' 'I would consider it only if it has second-line treatment in it'
	No (n=4)	'As long as inhibitors have not been conclusively proven to be effective, I don't want anything' 'I would consider it if a second-line treatment was given in the device'
Evidence is needed on efficacy:		
	Yes (n=0)	
	Maybe (n=6)	'I want to see trial results first, but it sounds ideal' 'It depends on the experiences of other MS patients and what my neurologist can tell me about it'
	No (n=0)	
Side effects (n=19)	Yes (n=7)	'No skin lesions' 'I assume the implant releases the medication spread out over the day, and this differs from taking a pill where the sudden overdoses gives me side effects'
	Maybe (n=6)	'It depends on the side effects, in doubt because INF-B is known for its side effects' 'Perhaps with a better dosage the side effects will be less'

	No (n=6)	'I got sick from taking INF-B' 'My veins closed when a Port-A-Cath was inserted'
Bodily integrity (n=11)	Yes (n=0)	
	Maybe (n=9)	'I don't like it that my body will be cut open' 'No more control over when the treatment is administered'
	No (n=2)	'I do not want a foreign object in my body'

N= the number of quotes found per topic, MS: multiple sclerosis.

DISCUSSION

This study aimed to understand the treatment decision-making process given the current treatment landscape, and to explore the possible acceptance of a new mode of administration, namely the Optogenerapy implant. The treatment decision-making process for persons with MS is a push-and-pull between uncertainty and the need for control. The uncertainty of living with MS may be somewhat reduced by controlling the disease via the use of a DMT. The Optogenerapy implant may possibly be a (medical technological) solution to reduce that uncertainty. Medical technology developers within the care of MS, and beyond, should be aware of these uncertainties and cater to these needs.

Patients face uncertainty in illness due to the complexity of the disease, its unpredictability and lack of information. (168) Coping mechanisms may be used to deal with such issues. Participants of the focus group sessions mention that receiving the diagnosis of MS provided temporary relief because a label could be placed on their symptoms. However, reducing uncertainty through diagnosis is not the same as a cure, and patients may remain uncertain because of a greater awareness of the fragility of their bodies. (169–171) Any coping mechanisms that are used may differ depending on the stage of the disease, in which emotional-based coping develops into a more active and adaptive strategy over time (172). Patients may address this uncertainty by undergoing treatment at some point during their disease, as done by our participants and also found elsewhere. (170,173,174)

Stakeholders involved in the development of medical technology should be aware that having an implantable device in one's body changes one's self-perception. Not only may technology affect one's social being, (175) it shapes the experience of illness. (176) Technology inserted into the body, such as neuromodulatory technology or implantable cardiovascular devices, changes how the body is viewed by a patient because the devices can affect and may take over certain processes within the body (for example spinal cord stimulation or cardiac rhythm). (176–178) Thus, both the developers of a technology and patients receiving that technology have to understand that there is an intricate relationship between the body and technology which may affect the livability of the technology and how one accepts as part of their lives. (177) Therefore, the extent to which patients accept and incorporate implantable devices into their daily lives is uncertain. Consequently, this type of information should be gathered, evaluated, and re-evaluated continuously during the life cycle of a device to make sure the technology matches patient needs as well as possible.

Getting patients involved early in the device design and development has multiple benefits. Incorporating patients ensures that research is more likely to reflect the interest of the patient and improve the quality of the research by reflecting patient needs. (179,180) Furthermore, there is a general agreement from the industry, regulatory authorities and health technology assessment bodies to involve patients and understanding their preferences early on during technology development. (181–183) The design should not have a negative effect on their experience with the device. (177) So rather than a "technology-push" in which developers do not directly interact with the end user of a product, there should be a "demand pull" in which the technology should be designed to address the needs and preferences of the end user. (184)

Researchers need to study patient preferences in a systematic way to understand the needs and preferences of patients regarding treatment decisions and new medical technologies. One method to quantify such preferences are stated-preference techniques, such as discrete

choice experiments (DCEs). A DCE asks patients to choose between two or more treatment choices (or profiles) based on a set of attributes and attribute levels. (49) Previous studies have found that people with MS prefer treatments that delay disease progression, reduce relapses, and prefer oral and infusion modes of administration over injections. (185,186) Furthermore, they have low preference for DMTs with a high treatment risk, such as significant adverse events. (185) Our results indicate that the focus group participants and survey respondents would be interested in the device. Reasons include the avoidance of self-injection, ease of use, and potentially less confrontation with being ill. However, they also indicated that since INFβ is the working substance of the implant, the implant is more appropriate for persons with recently diagnosed MS. Furthermore, concrete results of efficacy and safety profile are needed before participants would consider switching to the implant. Patient preferences of a new mode of administration such as an implant using the DCE methodology has not yet been done in MS. The results from the focus group sessions can inform researchers which patients to recruit and what attributes to include when examining preferences of modes of administration.

A method to incorporate patient preferences in device development is via co-design sessions. In co-design end-users are involved in the design process and work together with developers, thereby developing a device that is tailored to the needs of the end-users incorporating their personal experiences and know-how of a disease. (187) Co-design has been used in improving MS healthcare services, (188,189) but not necessarily in product development, as seen in other disease areas. (190–192) Design development is an iterative process and input from end-users should be incorporated at various moments during design development and see multiple prototypes. (193,194) The results of our focus groups are informative and may be used as input to plan a co-design session. Furthermore, future research into co-design should follow a theoretical framework and may include various methods such as focus groups, brainstorm sessions, usability tests and interviews depending on the stage of development. (194)

The combined approach of the focus group study and online survey helped to understand the views of persons with MS regarding a novel mode of administration. It should be noted that the focus group participants attended only a short information session on the implantable device which may have been too short to enable a truly informed judgement. The online survey respondents were given a brief textual description of the survey, which may limit the interpretability of their open text answers. Furthermore, the focus group participants sometimes might have given socially desirable answers ('the implant is a way to improve quality of life') since the aims of the Optogenerapy consortium were shared. The views of 16 persons with MS are not enough to make representative conclusions for the whole MS community. However, we believe that combining the results with the survey provides valuable insights to use in further research and development. Follow-up steps could be stated preference methods and co-design sessions with patients and developers. These methods are not mutually exclusive and should instead be seen as complementary since they can add value to the design of a device.

This study has several limitations. Participants interested in attending the focus group sessions and learning more about the implant responded positively to the request, which could have resulted in selection bias. Prior to the start of the focus group session the Optogenerapy implant was introduced, which may have led to pro-implant bias. However, we think that the bias is limited because the patients were not disproportionately enthusiastic about the device and viewed it from various perspectives. Furthermore, the implant was the last topic of the focus group session, which meant that some time had elapsed between the introductory talk and discussion about the implant.

Secondly, 56% (9/16) of the focus group participants were currently no longer taking DMTs though had taken treatment in the past, which might have led to recall bias about what it was like to undergo treatment. However, the similarity between our study results and those found in previous MS focus groups studies (170,174,195) suggest that the views expressed by the patients were valid.

Thirdly, the results of the focus group sessions were based on the views of 16 Dutch persons with MS living in the Netherlands, that are older than the general MS population. However, we observed similar views from the focus groups compared to the open text answers from the online survey, thus we believe that the results are somewhat generalizable for the Dutch MS population. Nonetheless, the results should be interpreted cautiously when making statements about persons with MS from other countries.

Fourthly, the focus group population was older than patients who may opt for an implant (i.e. younger, more recently diagnosed, and eligible for INFβ). This was confirmed in the survey results (persons with shorter disease duration were more interested in the device). Therefore, it would be informative to have younger persons involved in future focus group or co-design sessions to compare their views to the results of this focus group study.

CONCLUSION

Uncertainty regarding disease and treatment course is ever present in the lives of persons with MS. Essentially, persons with MS want to have some form of control over their disease and treatment course. There is the potential for persons with MS to accept a new mode of administration, such as the implantable Optogenerapy device. However, patients will then have to accept letting go of the control and trusting that the device will do the work for them. New technologies within the field of MS, and healthcare in general, should be directed at the patients for whom this can potentially be life-changing and beneficial. More importantly, patients should be engaged early on in the design process and consistently thereafter to make sure that the device is tailored to their needs.

5

AN IMPLANTABLE DEVICE TO TREAT MULTIPLE SCLEROSIS: A DISCRETE CHOICE EXPERIMENT ON PATIENT PREFERENCES IN THREE EUROPEAN COUNTRIES

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ABSTRACT

Background: Persons with multiple sclerosis (MS) take their treatment via pills, injections or infusions. A novel mode of disease-modifying treatment administration, an implantable device, is under development. This study determined MS patient preferences for three modes of first-line treatment administration (implant, pills, injectables), and trade-offs regarding treatment characteristics.

Methods: A survey including a discrete choice experiment was conducted among MS patients in the Netherlands, France, and the United Kingdom. Respondents had to repeatedly choose between various treatment scenarios with four treatment characteristics: risk of relapse, reduction of disease progression, risk of side effects and mode of administration. Data was analysed using a panel latent class logit model.

Results: Based on the preferences of 753 MS patients (response rate 7%: 753/11202), two latent classes were identified (class probability of 74% vs 26%). Persons with relapsing-remitting MS and who administered medication via injections generally preferred any treatment over no treatment. Patients who could walk without an aid were more likely to prefer no treatment. Reducing disease progression was the most important treatment characteristic class 1. Mode of administration was the most important characteristic in class 2. Patients were willing to accept an increase in risk of relapse and disease progression to get their treatment via an implant rather than injections. Predicted uptake was the highest for the implant, followed by pills, injections, and no treatment.

Conclusion: We found that a drug-delivery implant could be a potential addition to the MS treatment landscape: MS patients are willing to trade-off risk of relapse and disease progression for an implant, and predicted uptake for an implant is relatively high.

INTRODUCTION

Multiple sclerosis (MS) is an invalidating disease affecting 2.8 million people worldwide (196). MS has a chronic disease progression, which is immune-mediated and causes demyelination of the central nervous system affecting young adults, primarily women. The presentation of MS varies dependent on the location of the lesions and progression of the disease. Clinical features include physical dysfunctions (such as mobility and sensory problems) and cognitive decline (51). Patients can progress from a single clinical event suggestive of MS (a clinically isolated syndrome; CIS) into relapsing-remitting MS (RRMS) (51). Roughly 85% of patients are diagnosed with RRMS which is characterised by relapses (i.e. neurological dysfunctions) with full or partial recovery. The remaining patients may have disease progression from onset (diagnosed with primary progressive MS: PPMS) or have disease progression after having RRMS (diagnosed with secondary progressive MS: SPMS) (51).

The current treatment landscape is diverse and patients can be treated with multiple first- and second-line disease-modifying treatments (DMTs) that can be either injected, taken orally, or via infusion therapy (8). However, DMTs are not able to cure MS. DMTs may reduce disease progression and relapse rate, are associated with various (serious) adverse events and each mode of administration has their own frequency of administration (8). Consequently, patients have the difficult task of trading-off these different aspects of the therapy once deciding on starting a DMT.

Preference studies allow researchers to quantify patient preferences towards treatment decisions, thereby identifying the relative importance of health outcomes related to such a treatment decision (197). As such, patient needs can be quantified and analysed. Stated preference (SP) studies, such as discrete choice experiments (DCEs), have gained popularity within the field of MS (49). When performing a DCE, patients are asked to evaluate hypothetical MS treatment profiles based on a set of characteristics of treatment (attributes) and variants of these characteristics (attribute levels). Systematic reviews on this topic have identified that patients have a preference for treatments with a low risk of side-effects and treatments that delay disease progression along with reducing relapses. Moreover, patients prefer oral and infusion modes of administration over injections (185,186).

The Optogenerapy consortium, a European Horizon 2020 project, is developing a novel mode of fist-line DMT administration for MS patients (27,163). The Optogenerapy drug delivery implant releases beta-interferon (INF-β) into the body. The treatment is generated by genetically modified cells that produce INF-β confined within a chamber sealed by a porous membrane, which allows the device to be easily implanted or removed (27). The implant is a new mode of administration and can potentially replace standard injectable first-line INF-β delivery. Since this implant may possibly be an addition to the current treatment landscape within the field of MS, it is expected that patients will face tough trade-offs concerning the new mode of administration, which makes it an interesting area for research into patient preferences. Furthermore, patient preference information can inform about the (unmet) needs of patients, guide the product development, cost-effectiveness analysis and market authorisation (182,183,198). As such, the implant can be tailored to the needs of the patient, which may enhance patient satisfaction, lead to better health and more efficient healthcare systems (199).

The results of this study are of relevance for healthcare professionals, persons involved in medical technology development, and policy makers. Patient preference information may help healthcare professionals improve the shared decision-making with patients since patient and healthcare professionals treatment preferences can differ substantially (200–204). Also, patient preference information can guide and improve product development (205). Since such a device is new and the therapy released by the implant is INF-β, it is of interest to examine the relative desirability of this mode of administration compared to standard modes of first-line administration options for RRMS patients with comparable efficacy and safety profiles (pills or injectable therapy). We choose to not include infusion therapy as a mode of administration because it is usually given

as a second-line therapy (9,10). To our knowledge, no preference study has been performed examining an implantable device within the MS treatment landscape. Hence, the aim of this study is to quantify patient preferences for three modes of treatment administration (implant, pills, injections) and assess which trade-offs patients with MS are willing to make regarding treatment characteristics.

MATERIALS AND METHODS

Discrete choice experiment

This study used an online survey containing a discrete choice experiment (DCE) to elicit patient preferences for attributes of MS therapies in three Western European countries (the Netherlands, France, and the United Kingdom). The three countries were chosen because of the high prevalence of MS in the three countries (1 in 700 persons have MS in the Netherlands and in France, and 1 in 500 persons have MS in the United Kingdom), while taking study feasibility into account (location of members of the Optogenerapy consortium) (206–208). In DCEs, respondents choose between pairs of hypothetical treatment profiles, defined by their characteristics (attributes, such as risk of relapse) and with varying levels of that attribute (such as 30% or 70% less risk of relapse), in a series of questions, called choice tasks (197,209). Each choice task consists of a prespecified number of alternative treatment profiles with varying attribute levels (see Figure 1). By repeatedly presenting different treatment profiles in the choice tasks, and asking the respondent to choose the profile they most prefer, it is possible to determine the relative importance of the attributes (and levels) to one another (197). Using statistical methods that have a foundation in random utility theory, a DCE enables empirically studying relative importance between treatment attributes, while also taking into account patient characteristics (210).

Attributes and levels

The attributes and attribute levels concerning MS treatment were derived from systematic literature reviews (185,186) and were verified (i.e. cross validated) during two focus group sessions with MS patients (N=16) held in the Netherlands and by consulting two French MS specialists (211). Efficacy and safety were important themes identified in the focus group sessions (211) and combined with the results of the systematic reviews (185,186) the following four attributes were identified: risk of relapse, reducing disease progression, risk of side effects, and mode of administration. The attribute levels were chosen to capture the range of plausible outcomes of DMTs currently available on the market and the assumed health outcomes of the implant. In addition to side effects of DMTs described by the Dutch pharmacotherapy guidelines (212) we also included an adverse event specifically related to the implant, namely post-operative wound infection. A full description of the attributes and its levels can be found in Table 1 and Appendix A.

Table 1 Attributes and levels of the discrete choice tasks

Attribute	Attribute Level
Risk of relapse	- 30% less risk - 50% less risk - 70% less risk
Reducing disease progression	- 20% less disease progression - 40% less disease progression - 60% less disease progression
Risk of side effects	- Very common mild side effects (more than 10% risk) - Common moderate side effects (1 to 10% risk) - Rare severe side effects (0.1 to 1% risk)
Mode of administration	- Injecting treatment once a week - Injecting treatment 3 times per week - Taking 1 pill per day orally - Taking 2 pills per day orally - Replacing the implant once a year - Replacing the implant every 3 years

DCE design and questionnaire

The questionnaire was designed and developed following good research practices (209,213). Presenting all the selected attributes and attribute levels to a respondent would result in an unfeasibly large number of alternatives to be evaluated by the respondent. Hence, to reduce the number of alternatives while still being able to estimate the parameters of interest in a reliable way, a subset of alternatives was selected using a Bayesian D-efficient design as generated by Ngene software (214,215). To increase statistical efficiency of the Dutch design, prior estimates of the parameters were updated after the pilot data was collected (n=100 respondents) (214). The questionnaire in the United Kingdom and France contained the same updated design to eliminate possible differences in preference outcomes between the countries resulting from the design.

We created a design of 30 choice tasks that were divided into two blocks of 15 to reduce respondent burden. Thus, per questionnaire version each respondent was presented with 15 choice tasks rather than 30. Each choice task consisted of three alternatives: two alternatives ('Treatment 1' and 'Treatment 2') were characterised by a selection of attribute levels and the third alternative ('No treatment') allowed respondents to not choose any of the presented alternatives (opt-out). We included this opt-out alternative since – as in real-life – MS patients may actively choose not to take any DMTs. An example of a choice task can be found in Figure 1.

In addition to the 15 choice tasks described above, the questionnaire contained questions about patient demographics, health status, numeracy skills (216,217) and health literacy (218,219). Patient demographics were dichotomised for later analyses, for example into MS type (RRMS vs. CIS, PPMS and SPMS and 'I do not know'), treatment course (taking 1st-line injectable DMT vs not taking a 1st-line injectable DMT[1]), partner (married and partnered vs. unmarried, divorced, and widowed) and higher education (university vs. primary, secondary, vocational/technical education and other). Health status was measured using the EuroQoL 5 Dimensions questionnaire (EQ5D-5L) using country specific tariffs (134,135,137,138). Furthermore, respondents were asked whether they would or would not be interested in having the implant as a mode of administration. Finally, six concluding questions about perceived difficulty and length of the questionnaire and treatment options (5-point scale: strongly agree to strongly disagree), and six questions on the extent to which

[1] Patients were asked about current and past treatment course, choosing amongst the following 12 therapies: injectables (intramuscular interferon beta (INFβ) 1x per week, subcutaneous (s.c.) INFβ 3x per week, s.c. INFβ once every 2 weeks, s.c. INFβ once every 2 days, or glatiramer acetate), oral (dimethyl fumarate, cladribine, teriflunomide, or fingolimod), or infusion therapy (alemtuzumab, natalizumab, ocrelizumab).

they believe the COVID-19 pandemic affected their responses were asked (5-point scale: no influence to extreme influence).

The questionnaire was pre-tested using the think-aloud method in four Dutch MS patients. They were asked to read and think aloud while completing the questionnaire (209). The respondents indicated that the questionnaire was clear, the length was manageable, and that treatment trade-offs were accurately reflected.

After data collection was completed in the Netherlands, the questionnaire was translated to English and French. Translation to English was done by the researchers. Translation to French was done by a translation agency. Furthermore, native speakers working in health economics who were not involved in this study checked the translations and performed back and forward translation for the attributes and levels.

Figure 1 Example of a choice task

	Treatment 1	Treatment 2	No treatment
Risk of relapse	30% less risk	70% less risk	Unknown
Reducing disease progression	20% less progression	60% less progression	No reduction in disease progression
Risk of side effects	Very common mild side effects (more than 10% risk)	Common moderate side effects (1 to 10% risk)	No side effects
Mode of administration	1 pill per day	Replacing the implant 1 time per year	None
I choose:	○	✓	○

Data collection and study sample

Inclusion criteria were persons older than 18 years of age, diagnosed with MS (either CIS, RRMS, SPMS or PPMS), living in the Netherlands, France or the United Kingdom. Only respondents that gave written informed consent were included in the study. Fast responders (<7 minutes) who provided nonsensical answers (i.e. gibberish) in open field texts that did not require a response, and duplicates were excluded.

Respondents were recruited via a commercial survey sampling company Survey Engine. In addition to data collection via panels, patients were also recruited via national patient advocacy groups. All respondents received financial compensation upon completion of the questionnaire (€0.50 - €5). The exact amount depended on the channel and country of recruitment. In the Netherlands, data was collected in the first two weeks of August 2020. In the UK and France, data was collected between September and November 2020[2]. The study was approved by the Medical Ethical Testing Committee of the Erasmus Medical Centre (MEC-2019-0248).

Statistical analyses

The choices respondents made in the DCE were used to assess which trade-offs patients were willing to make regarding mode of administration (implant, pills or injections) and other treatment characteristics. The data from the Netherlands, France and the United Kingdom were pooled, and

[2] Due to a technical error, respondents in the UK did not see all questions regarding their current and past treatment course. Some respondents were successfully recontacted about this (n=72). Respondents who could not be recontacted were resampled (n=180).

a country-specific dummy variable was included in the analyses to assess potential differences in preferences between countries.

A main-effects multinomial logit model (MNL) was used as a starting point for model specification. We tested for linearity and higher order polynomials to determine the optimal model specification. To capture heterogeneity in patients' preferences, a panel latent class multinomial logit model was used. This panel type of model accounts for the multitude of choices each respondent made (i.e. 15 choice tasks per respondent) and assumes subgroups of respondents with different preferences between latent classes, but homogenous preferences within a class. We do not know how many latent (unobservable) classes there are within the population and each class has its own preference (utility function). However, we can group respondents with similar preference utilities within classes. This is based on the observable data collected, i.e. the individual responses to the choice tasks and respondent's background demographics. The number of latent classes in which to group the respondents can in theory be between one and the number of individuals in the population (220). To determine optimal number of latent classes, a range of 2-4 classes were tested using likelihood ratio tests and considering class size and interpretability.

The final model (counterbalancing model fit and interpretability) was a two-class model, with two linear and two categorical attribute levels and two alternative specific constants to correct for the order in which the alternatives were presented (left-right bias) and treatment opt-out. The detailed utility function can be found in Appendix B. In addition, to provide insight into the likelihood of respondents belonging to a particular latent class of preferences, twelve patient characteristics were included as covariates one-by-one in a so-called class assignment model. Covariates were only included in the final model if they significantly contributed to the class assignment model ($p<0.05$). We tested the contribution of the following categorical parameters to the class assignment model: country (France/UK/the Netherlands), male (yes/no), higher educated (yes/no), partner (yes/no), RRMS (yes/no), ability to walk without aid (yes/no), currently using injections (yes/no). The following continuous variables were dichotomized based on median split: age (≥45), long disease duration (≥ 10 years), high health utility (≥ 0.7), high EQ VAS (≥ 70), good health literacy (≥ 3 score), good numeracy (≥4 subjective score + objective scores correct). The final utility function of the class assignment model included relapsing-remitting MS, walking without an aid, currently using injections, and country of residence and can also be found in Appendix B. The choice analyses were performed using Apollo software version 0.1.0 (221,222).

The analyses resulted in parameter estimates (β) that indicate the relative importance of attributes and their levels. For the coefficients, the statistical significance ($p< 0.05$) indicated that respondents considered the attribute important in making their choices concerning MS treatment. The sign of the coefficient reflects whether the attribute(level) has a positive or negative effect on utility. These coefficients were used to examine which trade-offs respondents were willing to make, what the relative importance of attributes were, and what uptake is predicted for various modes of administration. Firstly, to illustrate which trade-offs respondents were willing to make to get treatment via an implant the maximum acceptable risk (MAR) was calculated. This was done by dividing the coefficient of implant replacement every three years by the coefficients of reduction in risk of relapse and reduction in disease progression, respectively. Secondly, the relative importance of attributes was assessed by taking the difference between the most and least desirable attribute level in each attribute, and dividing this by the sum of differences of all attributes (223). The larger this value, the larger the relative importance of an attribute. Thirdly, to compare desirability of different modes of administration, mean uptake was predicted for a set of four realistic alternative scenarios; three treatment options (for injections: administered once per week, risk of relapse = 30%, reduce disease progression = 40% and very common mild side effects; pills: 2 pills per day, risk of relapse = 50%, reduce disease progression = 40% and very common mild side effects; implant: replaced once per three years, risk of relapse = 30%, reducing disease progression = 40% and very common mild side effects) and one opt-out (no treatment, unknown risk of relapse, no reduction in disease progression and no side effects). These scenarios were

chosen to best reflect the efficacy and safety profile of INF-β (for the injections and implant) and oral therapy. Uptake was predicted by taking the exponent of the utility for the treatment scenario under evaluation divided by the sum of the treatment utility's exponent and the no treatment utility's exponent. Uptake was predicted for each class, and for the full sample by weighing the class probabilities.

RESULTS

Respondents

In total 753 respondents (the Netherlands n=250/1560, France n=256/5124, the United Kingdom n=254/4518) met the inclusion criteria, provided informed consent, and completed the questionnaire (response rate: 7% (760/11202)). Data collection ended as soon as the target of 250 respondents per country was reached (10 weeks in the Netherlands, 6 weeks in the UK, 5 weeks in France). Respondents were excluded if they completed the questionnaire in less than 7 minutes[3] and provided non-sensical answers (i.e. gibberish) in open questions that did not require a response. Duplicate responses were also excluded. These criteria led to the exclusion of five respondents in the French data (of which two duplicates), two in the English data (one non-sensical speeder and one duplicate)[4] and none of the Dutch respondents.

The characteristics of the patients are displayed in Table 2. The respondents had a mean age of 42 years, 68% were female, over half of the patients had RRMS (54%) and were able to walk without an aid (51%). There are somewhat less female respondents from France and the United Kingdom that completed the survey than you would expect to find in the French and UK MS population (we found 62% and 65.5% female respondents compared to country averages of 71% and 73% in France and the United Kingdom (207,208)). Furthermore, the patients in all three countries had somewhat more progressive disease than you would expect in the MS population (206–208), with an average of only 54% having RRMS. The vast majority were currently not taking a first-line injectable DMT. Significant differences were found between the countries for the abovementioned characteristics. Due to using different tariffs the mean health utility significantly differed between the countries and ranged from 0.48 in the United Kingdom, 0.63 in the Netherlands and 0.74 in France, though no significant differences were found in the EQ-VAS (mean score: 60.6).

Respondents generally found the survey easy (strongly agree: 47%) and one-third could have answered more questions (strongly agree: 35%). Most could easily choose between the hypothetical treatments presented to them (35% strongly agreed, 30% somewhat agreed). Three-quarters of respondents somewhat or fully understood the choices between the treatment options from the start of the survey (76%). More detailed results regarding the perception of the survey and the COVID-19 pandemic can be found in Appendix C (Table A1).

[3] Based on Dutch data, agreements were made with the survey sampling company about the exclusion of respondents. The cut-off of 7 minutes was set to be a third of the median completion time in Dutch data (21.4/3=7 minutes). In the Dutch data, 14 respondents completed the questionnaire in less than 7 minutes. In the English and French data, respectively, 32 and 25 respondents were faster than the cut-off. These were only excluded if they also provided non-sensical responses to questions that did not require a response.

[4] Because of a technical error 180 persons had to be resampled, before the resample, respondents were excluded if they met the following three exclusion criteria: 1) completed the questionnaire in less than 7 minutes, 2) reported to be diagnosed with MS under the age of 16, and 3) incorrectly responded to the objective numeracy questions. That led to the exclusion of 8 respondents in the UK data whom were not recontacted about their current DMT. Hence, 8 of 180 respondents that did not reply to the recontact attempt were not missing at random.

Table 2 Patient characteristics

	Total (n=753)	The Netherlands (n=250)	France (n=251)	The United Kingdom (n=252)[a]	P-value
Age, mean (SD)	42 (12.1)	43.3 (12.2)	39.2 (11.1)	43.6 (12.6)	<0.001[b]
Female, n (%)	512 (67.9)	191 (76.4)	156 (62.2)	165 (65.5)	0.002[c]
MS type					<0.001[c]
CIS	39 (5.2)	6 (2.4)	25 (9.9)	8 (3.2)	
RRMS	404 (53.7)	149 (59.6)	124 (49.4)	131 (51.9)	
PPMS	160 (21.3)	36 (14.4)	55 (21.9)	69 (27.4)	
SPMS	92 (12.2)	27 (10.8)	26 (10.4)	39 (15.5)	
I do not know	58 (7.7)	32 (12.8)	21 (8.4)	5 (1.9)	
Mobility status					<0.001[c]
Walk without an aid	386 (51.3)	159 (63.6)	118 (47.0)	109 (43.3)	
Walk with an aid	335 (44.5)	83 (33.2)	128 (51.0)	124 (49.2)	
Unable to walk	32 (4.3)	8 (3.2)	5 (1.9)	19 (7.5)	
Treatment course					0.002[c]
Taking 1st-line injectable DMT	142 (26.4)	31 (19.5)	74 (34.6)	37 (22.3)	
Not taking 1st-line injectable DMT	397 (73.7)	128 (80.5)	140 (65.4)	129 (77.7)	
Marital Status, n (%)					0.001[d]
Unmarried	164 (21.8)	58 (23.2)	62 (24.7)	44 (17.5)	
Partnered	105 (13.9)	41 (16.4)	44 (17.5)	20 (7.9)	
Married	427 (56.7)	130 (52.0)	126 (50.2)	171 (67.9)	
Divorced	50 (6.6)	20 (8.0)	16 (6.4)	14 (5.6)	
Widowed	7 (0.9)	1 (0.4)	3 (1.2)	3 (1.2)	
Education					<0.001[d]
Primary education	19 (2.5)	3 (1.2)	8 (3.2)	8 (3.2)	
Secondary education	169 (22.4)	64 (25.6)	38 (15.1)	67 (26.6)	
Vocational/technical education	201 (26.7)	86 (34.4)	56 (22.3)	59 (23.4)	
University	356 (47.3)	93 (37.2)	145 (57.8)	118 (46.8)	
Other	8 (1.1)	4 (1.6)	4 (1.6)		
Health utility, mean (SD)	0.62 (0.3)	0.63 (0.3)	0.74 (0.3)	0.48 (0.3)	0.004[b]
EQ VAS, mean (SD)	60.56 (20.3)	61.65 (20.3)	59.04 (21.7)	61 (18.9)	0.09[b]

CIS: clinically isolated syndrome, DMT: disease modifying therapy, EQ VAS: EuroQol visual analogue scale, PPMS: primary progressive multiple sclerosis, RRMS: relapsing-remitting multiple sclerosis, SD: standard deviation, SPMS: secondary progressive multiple sclerosis. [a]Due to a technical error, some respondents in the UK could not answer all questions regarding their current DMT. Some respondents were successfully recontacted about this (n=72). Respondents who could not be recontacted were resampled (n=180), [b]ANOVA, [c]Chi-2 test, [d]Fisher's exact test.

Discrete choice experiment

The optimal number of latent classes was two, with class probabilities of 76% for class 1 and 24% in class 2 (Table 3). All attributes in both classes, except the risk of side effects, had statistically significant estimates ($p<0.05$). In both classes, the negative constant for Treatment 1 indicates that respondents were less likely to choose the treatment alternative presented first as compared to the alternative that followed (i.e. right-left bias).

Patients in class 1 had a statistically significant negative coefficient for the alternative specific constant of no treatment, indicating that they generally preferred any treatment over no treatment, all else being equal. They preferred their treatment to provide less risk of relapse and less disease progression. Rare severe side effects were less desirable than very common mild side effects. Common moderate side effects were perceived not statistically different from very common mild side effects ($p=0.427$). As compared to the reference level of three injections per week, one pill per day was most preferred followed by an implant replaced every year, an implant replaced every three years, two pills per day, and injections once per week. Coefficient sizes of replacing the implant once a year and replacing it once every three years were relatively similar.
Patients in class 2, the smaller class, generally preferred no treatment. A lower risk of relapse and reducing disease progression was preferred and rare severe side effects were less desirable than very common mild side effects. Patients in this class were also indifferent between common moderate side effects and very common mild side effects ($p=0.169$). In this class the order of preference for mode and frequency of administration was like in class 1. However, the coefficient of pills twice per day was slightly higher than the coefficients for implants, whereas injections once per week were not statistically different from the reference level injections three times per week ($p=0.396$). Again, the coefficients of both frequencies of replacing the implant were relatively close, as was the coefficient of pills twice a day.

As shown by the class size, people were more likely to be in class 1. More specifically, patients with RRMS and who administered medication via injections had a higher probability to belong to this class. Patients who could walk without an aid were more likely to be in class 2 (i.e. negative coefficient in class 1 of class probability model). The country of residence was not statistically significantly related with class membership, indicating little differences in preference structure across countries that was not captured by any of the other covariates included in the class assignment model.

Table 3 Latent class results

	Class 1			Class 2		
	Coeff.	**Std.err.**	**P-value**	**Coeff.**	**Std.err.**	**P-value**
Constant (no treatment)	-0.405	0.110	<0.001	1.818	0.195	<0.001
Constant (Treatment 1)	-0.118	0.027	<0.001	-0.206	0.063	<0.001
Reducing risk of relapse	0.018	0.001	<0.001	0.007	0.002	0.001
Reducing disease progression	0.028	0.001	<0.001	0.012	0.003	0.000
Risk of side effects						
Very common mild side effects (Ref)	0.000	-	-	0.000	-	-
Common moderate side effects	0.008	0.044	0.427	-0.080	0.084	0.169
Rare severe side effects	-0.116	0.042	0.003	-0.170	0.087	0.025
Mode of administration						
Injections 3x per week (Ref)	0.000	-	-	0.000	-	-
Injections 1x per week	0.319	0.064	<0.001	-0.036	0.135	0.396
Implant 1x per year	0.483	0.057	<0.001	0.513	0.124	<0.001
Implant 1x per 3 years	0.481	0.061	<0.001	0.474	0.130	<0.001
Pills 2x per day	0.365	0.062	<0.001	0.521	0.127	<0.001
Pills 1x per day	0.672	0.061	<0.001	0.741	0.124	<0.001
Class probability model						
Constant	0.866	0.213	<0.001	-	-	-
Relapsing-remitting MS (yes)	0.525	0.187	0.003	-	-	-
Mobility (walk without an aid)	-0.382	0.191	0.023	-	-	-
Current DMT (injections)	0.572	0.212	0.004	-	-	-
Country (France)	-0.099	0.228	0.332	-	-	-
Country (The United Kingdom)	0.263	0.232	0.128	-	-	-
Average class probability (%)	76			24		
Log-likelihood	9491.48					
Akaike Information Criterion (AIC)	19038.95					
Bayesian Information Criterion (BIC)	19244.36					

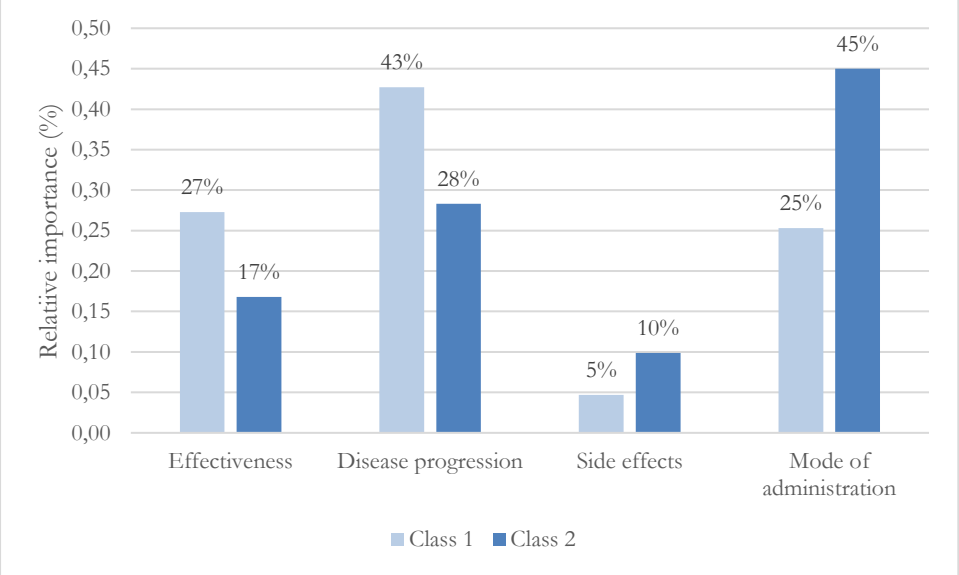
Coeff: Coefficient, DMT: disease modifying treatment, MS: multiple sclerosis, Std.err.: Standard error, Ref: Reference level.

Maximum acceptable risk, relative importance and predicted uptake

The maximum acceptable risk for respondents in class 1 was a 27%[5] increase in risk of relapse to get their treatment via an implant that is replaced once per 3 years rather than injections 3 times per week, all else equal. In class 2, this maximum acceptable risk was 65%. In terms of disease progression, again all else equal, respondents in class 1 were willing to accept 17% disease progression to get their treatment via an implant (replacement once per 3 years), rather than injections 3 times per week. In class 2, this was 39%.

Relative to the other attributes, reducing disease progression was the most important attribute in class 1, while risk of side effects was the least important attribute (Figure 2). In class 2, mode of administration was the most important attribute, while side effects were least important.

Figure 2 Relative importance of attributes based on latent class results



The mean predicted uptake was on average highest for the implant (43%), followed by pills (26%), and injections (21%) when comparing the different modes of administration and their accompanying treatment characteristics (Table 4). Eleven percent of the full sample would not choose any treatment. When comparing uptake of modes of administration between classes, the implant is most desirable in both classes (47% in class 1 and 30% in class 2). The uptake of pills was also relatively similar (27% vs. 20%). The largest relative difference in predicted uptake between classes was for injections, with 23% uptake in class 1 and 12% in class 2. Furthermore, as was also seen by the sign of the alternative specific constant of no treatment in Table 3, predicted uptake was higher for every mode of administration in class 1 than in class 2. In class 2 38% respondents would choose no treatment.

[5] $27\% = \frac{\beta_{\text{mode of administration implant 1x per 3 years}}}{\beta_{\text{reduction risk of relapse}}} = \frac{0.481}{0.018}$, all other calculations of maximum acceptable risk were calculated in the same manner.

Table 4 Predicted uptake per mode of administration based on latent class results

Mode and frequency of administration	Scenario	Average	Class 1	Class 2
Implant 1x per 3 years	30% less risk of relapse, 40% less disease progression, Very common mild side effects	43%	47%	30%
Pills 2x per day	50% risk of relapse, 40% less disease progression, Very common mild side effects	26%	27%	20%
Injections 1x per week	30% less risk of relapse, 40% less disease progression, Very common mild side effects	21%	23%	12%
No treatment (opt-out)	Unknown risk of relapse, No reduction in disease progression, No side effects	11%	2%	38%

In the questions where respondents were asked whether they would or would not be interested in having the implant as a mode of administration, almost half (47%) reported yes, 19% said no, and 34% reported maybe being interested. Frequently mentioned reasons why persons would choose the implant are because it prevents them from having to inject themselves, persons forget to take their treatment, problems with taking oral therapy and ease of use. But before choosing such a device, respondents also mention that they would need to know about the efficacy and safety profile and need more information. Others are hesitant to have an implant in their body and the idea of needing an operation to do so. Furthermore, respondents also mention that they are content with their current treatment and find no need for the implant.

DISCUSSION

This study aimed to quantify the preferences and trade-offs MS patients were willing to make for three modes of treatment administration (implant, pills and injections) and focused on whether a novel implantable mode of administration may be accepted by patients given the treatment landscape. Two different preference structures were found that mostly varied in whether respondents would choose the treatments described to them (class 1, which had the largest probability) or not (class 2). As expected, in both classes patients preferred their treatment to reduce risk of relapse and disease progression, and the presence of rare severe side effects had a negative effect on treatment choice as compared to very common mild side effects. Reducing disease progression was the most important treatment characteristic in class 1, while mode of administration was most important for the group hesitant to take treatment. Risk of side effects was least important in both classes. Preferences for modes of administration differed per class, but it was observed that patients generally would be open to having an implant as a mode of administration. Patients were willing to accept an increase in risk of relapse and some disease progression to get their treatment via an implant rather than via injections. Furthermore, the mean predicted uptake was the highest for the implant, followed by pills, injections, and no treatment.

To our knowledge this is the first DCE performed examining an implant as an alternative mode of treatment administration for MS patients. However, research has been conducted in another neurological area. A DCE studying treatment preferences for device-aided modes of administration in Parkinson's Disease in the United States found that patients preferred a medicine pump over deep brain stimulation and oral treatment. Furthermore, the results showed that treatment outcomes such as efficacy and side-effects drove treatment choice, rather than the mode of administration (224). Our study provides first insights into patient preferences regarding implantable modes of treatment administration in MS, but future research in other (neurological)

fields where drug delivery is provided via an implantable device (for example diabetes or spasticity (225,226)) is warranted.

We found that the implant was the most desirable mode of administration (regardless of class allocation) with a mean predicted uptake of 43% for the whole population. Lynd et al. (2018) found that factors affecting uptake of a new DMT are efficacy and safety. Patients with MS would switch from an injectable to an oral therapy only if the DMT was at least as effective and safe as an injectable. Though, persons would not switch DMT for convenience reasons if that meant sacrificing efficacy or safety (195). In contrast, we found that patients would be willing to sacrifice some efficacy to switch from an injectable to implant. Although we found no significant differences in preference structure depending on health literacy and numeracy, we should be aware that understanding benefits and risks of treatment is difficult, and MS patients show poor objective risk-understanding and underestimate risks such as side effects (185), which may explain why patients would sacrifice efficacy or safety. Nevertheless, patients mentioned that more information on efficacy and safety was needed before choosing an implant. Also, physicians, rightly so, may not encourage persons to switch to a less efficacious DMT because of the impact of relapses and progression on the quality of life of patients. Physicians should evaluate patient preferences and shared decision-making is important when deciding on the most appropriate DMT for the patient (54). Overall, our results suggested that the implant may fit quite nicely into the current mode of treatment administration landscape and persons with MS would be willing to choose this alternative when presented to them.

Our result of patients preferring efficacious treatment and oral therapy over injectable DMTs is in line with previous research examining the preferences of MS patients (186). In both classes we found that rare severe side effects were significantly less preferred than mild common side effects, and patients were indifferent between mild and moderate side effects. However, regardless of class allocation the safety profile (side effects) was the least important attribute relative to the other attributes. This contrasts to what is usually reported (57,61,227). As mentioned above, one should take into account the complexity of interpreting risks as a possible explanation for the fact that the safety profile was deemed to be the safety profile as the least important attribute.

We found differences in preferences according to current DMT (taking a first-line injectable DMT yes or no, where 'no' contained persons on oral or IV therapy). A multi-country DCE study performed by Bauer et al (2020) stratified MS patient preferences by current DMT. They found that treatment preferences differed depending on current mode of administration. Among persons currently on injectable DMT, the mode and frequency of administration was significantly less important compared to those currently on IV therapy or oral therapy (228), similar to our results. Furthermore, they found that the safety profile was generally the second the most important attribute to patients regardless of mode of administration, dissimilar to our results. Additionally, persons not currently on injectable DMTs, with progressive forms of MS, and who are mobile are more likely to choose no treatment (class 2). Persons in class 2 find it important to reduce risk of relapse and disease progression, however, we can imagine that these persons have had some (extensive) treatment experience in the past and therefore, now, no longer prefer to have treatment. In a focus group study amongst Dutch persons with (progressive) MS, negative treatment experiences such as adverse events and doubts about efficacy were reasons why they were currently no longer DMTs (211), and this may hold for the respondents of the DCE also.

For the further development of the Optogenerapy implant, it is advised to extend the research with follow-up sessions with MS patients and involve them in the development and validate mock-ups of the device by using these results as a starting point. Also, patient preference information should be incorporated in future health technology appraisals because that information can help guide whether a new technology should be approved for an entire population or only for certain patient subgroups for which there are notable positive health outcomes (183,198).

Our study has several strengths. To our knowledge, we were the first to examine the potential uptake of an implantable mode of treatment administration for MS patients. We followed good research practices and therefore performed a literature search and used qualitative methods, such as focus groups, for the attribute and level development. While this is advised (49), it is not always done (186). In the focus groups we did a preliminary examination of the views towards treatment preferences and the implantable device, and this DCE has validated those results found. Furthermore, respondents from three different countries were included in the study so the results are a good starting point to examine implantable preferences in other countries and compare those results to ours.

This study has some limitations. Firstly, patients were recruited via online panels and patient advocacy groups in three Western countries. As such, the MS diagnosis was self-reported and only respondents with access to the internet were recruited. Also, although patients are generally more engaged in DCEs compared to the general public (229), response rate was low. These factors may potentially lead to information and selection bias and limited generalizability to other countries. Secondly, though we followed good research practices we did not consult with UK-based MS specialists due to practical constraints. As a consequence, the scope of DMTs that we included might be limited, because the NHS treatment pathway includes infusion therapies as a first-line treatment for highly active RRMS (230). Additionally, due to practical issues, the pre-test was based on four Dutch MS patients and we did not pre-test in France or the United Kingdom. Furthermore, the priors were based on the pilot performed in the Netherlands and those were set equal for all three countries to enhance comparability of the survey results. However, the respondents from countries differed in some background characteristics. As such, it is possible that patients in different countries responded differently. However, we found no differences in preference structures by country of residence, suggesting the validity of the DCE is intact and therefore we do not think these choices had a great effect on the outcomes. Finally, we examined the preferences and uptake with efficacy and safety profiles most similar to first-line injectable therapies, however most of our patients were taking other treatments, thus perhaps not reflecting their true needs. Nevertheless, patients still preferred the implant, and perhaps this mode may be even more preferred if the efficacy rates are more similar to infusion therapy or second-line treatment (for example, 50%-70% less risk of relapse or 40%-60% less disease progression and potentially more risk of side effects). Future preference studies including the treatment profiles of DMTs such as infusion therapies are needed to make a more comprehensible comparison to the entire treatment landscape.

CONCLUSION

The novel implantable drug delivery device may potentially be an addition to the treatment landscape for persons with MS, and to our knowledge, this was the first stated preference study to examine this possibility. Patients preferred efficacious treatment over side effects. Patients are willing to sacrifice some treatment efficacy to switch from injectable treatment to the implant, though this should be interpreted cautiously because it is difficult for persons to understand the benefit-risk trade-off. Preferences differed per type of MS, current DMT, and mobility. Collecting patient preference information at a timely manner and at multiple phases of medical technology development is important to align the needs of the patient to the technology. Further research is needed to examine the position of the implant compared to infusion therapy.

APPENDIX

Appendix A Description of the attributes and levels presented to the respondents

Part 2: Questions about treatment characteristics

In the next part of the survey you will be presented with 8 choices on MS treatments. We are interested to know which of the treatments you would prefer. There are no right or wrong answers. You will be asked to make a choice between the different treatment options presented. The treatment options may seem very similar, but the little differences make that it is important for us that you answer all the questions carefully and completely.
Below you will find an explanation on four characteristics relating to the MS treatments in this study. Please read this carefully. Afterwards you will get some example questions.

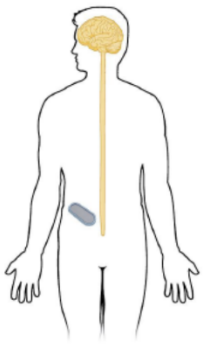
Risk of relapse: Multiple sclerosis is a disease characterized by relapses (also known as an exacerbation or a flare-up). An MS treatment may reduce the risk of a relapse. The risk of a relapse, in comparison to no treatment, differs per treatment and may have the following values, such as:

- 30% less risk of getting a relapse (in comparison to no treatment)
- 50% less risk of getting a relapse (in comparison to no treatment)
- 70% less risk of getting a relapse (in comparison to no treatment)

Reducing disease progression: Multiple sclerosis is a disease that causes damage to the brain and spinal cord. The nerves become damaged and are less capable of transmitting signals to and from the brain. Consequently, you may suffer from nerve damage. Reducing the risk of disease progression (also known as worsening), in comparison to no treatment, differs per treatment and may have the following values, such as:

- 20% less disease progression (in comparison to no treatment)
- 40% less disease progression (in comparison to no treatment)
- 60% less disease progression (in comparison to no treatment)

Mode of administration: MS treatments can be administerd in different ways. In this study we will examine three different modes of administration: injecting the treatment, taking the treatment orally via a pill, and receiving the treatment via an implant.



You may take the *pill* any moment of the day orally. The frequency of administering the pill differs per treatment option.

The *injectable* treatments are provided via a pre-filled syringe. The frequency of administering the injection differs per treatment option.

The *implant* is a medical device (6cm x 2cm x 0.2cm; imagine a thin USB stick). The implant is placed by the surgeon at the outpatient clinic and is implanted underneath the skin in the lower back (see image). The implant releases the MS treatment, with the correct dosage, into your body. You do not have to administer the treatment yourself, meaning no injections or pills are needed. The implant will be replaced every so often.

The mode and frequency of administration differ per treatment and may have the following values, such as:

- Injecting treatment 1 time per week
- Injecting treatment 3 times per week
- Taking 1 pill per day orally
- Taking 2 pills per day orally
- Replacing the implant 1 time per year
- Replacing the implant 1 time every 3 years

Risk of side effects: MS treatment may be associated with a risk of developing mild and severe side effects. The risk of developing side effects differs per treatment option.

Very commonly ocuring mild side effects are flu-like symptoms, gastro-intestinal symptoms and injection-site reactions (occur in more than 10% of all patients).
Commonly occuring moderate side effects are headache, fatigue, dizziness, and urinary tract or respiratory infections (occur in 1 to 10% of all patients).
Rarely occuring, severe (possibly life threatening) side effects are an infection of the brain (progressive multifocal leukoencophalopathy), liver toxicity and post-operative wound infection (occur in 0.1 to 1% of all patients).

The risk of developing the side effects differ per treatment option and can have the following values, such as:

- Very common mild side effects (more than 10% risk)
- Common moderate side effects (1 to 10% risk)
- Rare severe side effects (0.1 to 1% risk)

Appendix B Utility functions.

The utility function was specified as follows:

$V(treatment\ 1)_{nsj|c}$

$$= \beta_{0|c} + \beta_{1|c} \text{ reduction risk of relapse}$$
$$+ \beta_{2|c} \text{ reduction of disease progression}$$
$$+ \beta_{3|c} \text{ risk of side effects}_{\text{common moderate nsj|c}}$$
$$+ \beta_{4|c} \text{ risk of side effects}_{\text{rare severe nsj|c}}$$
$$+ \beta_{5|c} \text{ mode of administration}_{\text{injections 1x per week nsj|c}}$$
$$+ \beta_{6|c} \text{ mode of administration}_{\text{implant 1x per year nsj|c}}$$
$$+ \beta_{7|c} \text{ mode of administration}_{\text{implant 1x per 3 years nsj|c}}$$
$$+ \beta_{8|c} \text{ mode of administration}_{\text{pills 2x per day nsj|c}}$$
$$+ \beta_{9|c} \text{ mode of administration}_{\text{pills 1x per day nsj|c}}$$

$V(treatment\ 2)_{nsj|c}$

$$= \beta_{1|c} \text{ reduction risk of relapse}$$
$$+ \beta_{2|c} \text{ reduction of disease progression}$$
$$+ \beta_{3|c} \text{ risk of side effects}_{\text{common moderate nsj|c}}$$
$$+ \beta_{4|c} \text{ risk of side effects}_{\text{rare severe nsj|c}}$$
$$+ \beta_{5|c} \text{ mode of administration}_{\text{injections 1x per week nsj|c}}$$
$$+ \beta_{6|c} \text{ mode of administration}_{\text{implant 1x per year nsj|c}}$$
$$+ \beta_{7|c} \text{ mode of administration}_{\text{implant 1x per 3 years nsj|c}}$$
$$+ \beta_{8|c} \text{ mode of administration}_{\text{pills 2x per day nsj|c}}$$
$$+ \beta_{9|c} \text{ mode of administration}_{\text{pills 1x per day nsj|c}}$$

$V(optout)_{nsj|c} = \beta_{10|c}$,

where $V_{nsj|c}$ is the observed utility of participant *n* in class *c* for choice set *s* for alternative *j*. The constant $\beta_{0|c}$ and $\beta_{10|c}$ represent the alternative specific constants for respectively the alternative that was presented first, and last (i.e. the opt-out). $\beta_{1|c}$ to $\beta_{9|c}$ indicate the class-specific parameter weights (or coefficients) of each attribute level. Reference levels are not included in the utility function and can be found in Table 3.

The final class assignment utility function was:

$V_{n|c} = \beta_{0|c} + \beta_{1|c} \text{ relapsing remitting MS}_{\text{n}} + \beta_{2|c} \text{ walk without an aid}_{\text{n}} +$
$\beta_{3|c} \text{ injections}_{\text{n}} + \beta_{4|c} \text{ France}_{\text{n}} + \beta_{5|c} \text{ United Kingdom}_{\text{n}}$.

Appendix C Concluding questions and influence of COVID-19

	Total population		The Netherlands		France		The United Kingdom	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Concluding questions								
The survey was easy:								
Strongly agree	355	47.1	87	34.5	144	57.4	124	49.6
Somewhat agree	178	23.6	73	28.9	49	19.5	56	22.4
Neutral	141	18.7	64	25.4	28	11.2	49	19.6
Somewhat disagree	77	10.2	27	10.7	30	12.0	20	8.0
Strongly disagree	2	0.3	1	0.4			1	0.4
I could have answered more questions:								
Strongly agree	262	34.8	61	24.2	97	38.7	104	41.6
Somewhat agree	169	22.4	72	28.6	54	21.5	43	17.2
Neutral	183	24.3	60	23.8	54	21.5	69	27.6
Somewhat disagree	95	12.6	47	18.7	28	11.2	20	8.0
Strongly disagree	44	5.8	12	4.8	18	7.2	14	5.6
I could easily choose between the treatments:								
Strongly agree	268	35.6	55	21.8	115	45.8	98	39.2
Somewhat agree	228	30.3	90	35.7	58	23.1	80	32.0
Neutral	151	20.1	78	31	38	15.1	35	14.0
Somewhat disagree	78	10.4	24	9.5	29	11.6	25	10.0
Strongly disagree	28	3.7	5	2	11	4.4	12	4.8
I fully understood the choices between the treatment options from the beginning:								
Strongly agree	404	53.7	95	37.7	129	51.4	180	72.0
Somewhat agree	169	22.4	75	29.8	55	21.9	39	15.6
Neutral	92	12.2	38	15.1	34	13.6	20	8.0
Somewhat disagree	71	9.4	39	15.5	25	10	7	2.8
Strongly disagree	17	2.2	5	2	8	3.2	4	1.6
I found some of the presented treatments difficult to imagine:								
Strongly agree	141	18.7	32	12.7	66	26.3	43	17.2
Somewhat agree	198	26.3	45	17.9	74	29.5	79	31.6
Neutral	178	23.6	72	28.6	51	20.3	55	22.0
Somewhat disagree	145	19.3	75	29.8	39	15.5	31	12.4
Strongly disagree	91	12.1	28	11.1	21	8.4	42	16.8
I found all treatment characteristics were equally important:								

Strongly agree	227	30.2	51	20.2	108	43.0	68	27.2
Somewhat agree	211	28.0	79	31.4	71	28.3	61	24.4
Neutral	164	21.8	72	28.6	41	16.3	51	20.4
Somewhat disagree	121	16.1	41	16.3	26	10.4	54	21.6
Strongly disagree	30	4	9	3.6	5	2	16	6.4
COVID-19 questions								
Do you think that the current situation with regards to the coronavirus has influenced your answers during the questionnaire?								
No influence	336	44.6	81	32.2	102	40.6	153	61.2
Some influence	148	19.7	45	17.9	44	17.5	59	23.6
Moderate influence	138	18.3	70	27.8	48	19.1	20	8.0
Severe influence	95	12.6	41	16.3	39	15.5	15	6.0
Extreme influence	36	4.8	15	6.0	18	7.2	3	1.2
Are you/ have you been infected with the coronavirus?								
No, I have been tested and had a negative result	204	27.1	58	23.0	107	42.6	39	15.6
Probably not, but I haven't been tested	446	59.2	138	54.7	112	44.6	196	78.4
Probably yes, but I haven't been tested	71	9.4	39	15.5	20	8.0	12	4.8
Yes, I have been tested and had a positive test result	32	4.3	17	6.8	12	4.8	3	1.2
I am at risk of being infected with the coronavirus								
No risk	33	4.4	5	2.0	12	4.8	16	6.4
Low risk	204	27.1	63	25.0	47	18.7	94	37.6
Somewhat at risk	298	39.6	119	47.2	86	34.3	93	37.2
High risk	159	21.1	48	19.1	74	29.5	37	14.8
Extremely high risk	59	7.8	17	6.8	32	12.8	10	4.0
I am at risk of getting sick once infected with the coronavirus								
No risk	26	3.5	5	12.0	11	4.4	10	4.0
Low risk	102	13.6	32	12.7	33	13.2	37	14.8
Somewhat at risk	270	35.9	84	33.3	91	36.3	95	38.0
High risk	251	33.3	96	38.1	70	27.9	85	34.0
Extremely high risk	104	13.8	35	13.9	46	18.3	23	9.2
I am at risk of dying once infected with the coronavirus								
No risk	48	6.4	4	1.6	20	8.-0	24	9.6
Low risk	221	29.4	72	28.6	52	20.7	97	38.8
Somewhat at risk	252	33.5	89	35.3	83	33.1	80	32.0
High risk	153	20.3	60	23.8	57	22.7	36	14.4
Extremely high risk	79	10.5	27	10.7	39	15.5	13	5.2
Are you concerned becoming infected with the coronavirus?								

I am not concerned	45	6.0	8	3.2	14	5.6	23	9.2
I have little concern	118	15.7	24	9.5	39	15.5	55	22.0
I have some concern	278	36.9	100	39.7	65	25.9	113	45.2
I have many concerns	213	28.3	84	33.3	81	32.3	48	19.2
I am extremely concerned	99	13.2	36	14.3	52	20.7	11	4.4

Concluding questions and the influence of the COVID-19 pandemic on responses.

PART III

THE "FINAL" ACT: WHAT IS THE POTENTIAL COST-EFFECTIVENESS OF THE CELL-BASED THERAPY DELIVERY IMPLANT IN MULTIPLE SCLEROSIS PATIENTS?

6

THE POTENTIAL COST-EFFECTIVENESS OF A CELL-BASED BIOELECTRONIC IMPLANTABLE DEVICE DELIVERING INTERFERON BETA 1A THERAPY VERSUS INJECTABLE INTERFERON BETA 1A TREATMENT IN RELAPSING-REMITTING MULTIPLE SCLEROSIS

L.A. Visser, M. Folcher, C. Delgado Simao, B. Gutierrez Arechederra, E. Escudero, C.A. Uyl-de Groot, W.K. Redekop. PharmacoEconomics (2021).

ABSTRACT

Background: Current first-line disease-modifying therapies (DMT) for multiple sclerosis (MS) patients are injectable or oral treatments. The Optogenerapy consortium is developing a novel bioelectronic cell-based implant for controlled release of beta-interferon (INFβ1a) protein into the body. The current study estimated the potential cost-effectiveness of the Optogenerapy implant (hereafter: Optoferon) compared with injectable INFβ1a (Avonex).

Methods: A Markov model simulating the costs and effects of Optoferon compared with injectable 30 mg INFβ1a over a 9-year time horizon from a Dutch societal perspective. Costs were reported in 2019 Euros and discounted at a 4% annual rate, health effects were discounted at a 1.5% annual rate. The cohort consisted of 35-year old, relapsing-remitting MS patients with mild disability. The device is implanted in a daycare setting, and is replaced every three years. In the base-case analysis, we assumed equal input parameters for Optoferon and Avonex regarding: disability progression, health effects, adverse event probabilities, and acquisition costs. We assumed reduced annual relapse rates and withdrawal rates for Optoferon compared to Avonex. Sensitivity, scenario, value of information, and headroom analysis were performed.

Results: Optoferon was the dominant strategy with cost reductions (-€ 26,966) and health gains (0.45 quality adjusted life years gained). A main driver of costs differences are the acquisition costs of Optoferon being two-and-a-half times less than the costs of Avonex. The incremental cost effectiveness ratio was most sensitive to variations in the annual acquisition costs of Avonex, the annual withdrawal rate of Avonex and Optoferon, and the disability progression of Avonex.

Conclusion: Innovative technology such as the Optoferon implant may be a cost-effective therapy for patients with MS. The novel implantable mode of therapeutic protein administration has the potential to become a new mode of treatment administration for MS patients and in other disease areas. However, trials are needed to establish safety and effectiveness.

INTRODUCTION

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system. The disease has a prevalence in Europe of 60-120 per 100,000, and 120-150 per 100,000 in North America (123). Roughly 70% of the persons diagnosed are women, and the age of diagnosis ranges between 20 - 40 years. The most prevalent type of MS is relapsing-remitting MS (RRMS), where patients suffer from periods of neurological dysfunction, known as relapses, alternated with periods of remission (51). Examples of MS-related roblems include vision loss, limb weakness, or erectile dysfunctions. Patients with MS have a high disease burden (23) and lower quality of life (QOL) compared to the general population and patients with other chronic diseases (124,231). The lower QOL may be due to the unpredictable disease course and the limited curative effects of the disease-modifying therapies (DMTs) available (47).

Currently available DMTs can reduce relapse rate and disease progression, however, are also associated with adverse events, thereby resulting in problems with non-adherence. For example, adverse events associated with the first-line DMT interferon-beta (INF-β) are injection-site reactions, flu-like symptoms and lipoatrophy (8,9). Patients experiencing adverse events can become non-adherent to injectable treatment, discontinue therapy, or switch to other first or second-line DMTs (186). Although patients are well aware of the importance of treatment, non-adherence to treatment is a well-known problem acknowledged by both MS patients and health care providers (232), and may have both unfavorable clinical and economic consequences. Clinically, non-adherence reduces treatment efficacy thereby increasing risk of relapses (233). Moreover, from an economic viewpoint, MS patients non-adherent to INF-β treatment tend to have more hospital admissions, emergency room visits and outpatient clinic visits than adherent patients (233).

A solution to improve non-adherence and thereby the health outcomes of MS patients can be found in cell therapy delivery vehicles. Cell therapy delivery vehicles are implantable devices that mediate the action of therapeutic cells by integrating confined genetically programmed cells to control the secretion of a therapeutic protein in the body (27). The Optogenerapy consortium, a European Horizon 2020 project, is developing a cell therapy delivery vehicle for MS patients classified as a combined advanced therapy medicinal product (ATMP). The device integrates optogenetic programmed cells (cells that are genetically modified to release INF-β 1a in response to near-infrared light) for controlled release INF-β 1a protein into the body via a semi-permeable membrane (27,234). The optogenetics interface controls the cellular behavior of the cells and is powered wirelessly (27).

The consortium aims to improve QOL of patients, improve treatment efficacy, and tackle non-adherence by developing this new mode of administration. The objective of this study was to estimate the potential cost-effectiveness of the Optogenerapy implant (hereafter: Optoferon) compared to injectable INF-β 1a treatment in early RRMS patients in the Netherlands.

METHODS

The Markov model estimated the potential cost-effectiveness of Optoferon compared to injectable INF-β 1a treatment Avonex (Biogen, Cambridge MA) in terms of quality-adjusted life years (QALYs) and costs included from the societal perspective. The main result was the incremental costs per QALY gained with Optoferon compared to Avonex in the Dutch healthcare setting.

Patients

Patient characteristics at baseline were a hypothetical cohort of 1000 Dutch RRMS patients. The baseline characteristics (mean starting age of the cohort was set at 35 years old, a 3:1 female to male ratio, and the distribution of disability status based on the patient's current first-line DMT status) reflect the data collected through an online HRQOL survey in the Netherlands (166). The disability status was measured using the Expanded Disability Status Scale (EDSS, a measure that quantifies disability on a scale from 0 (no disability) to 10 (death) (6)), and the distribution was as follows: EDSS 0 (14%), EDSS 1 (29%), EDSS 2 (29%), EDSS 3 (0%), EDSS 4 (0%), EDSS 5 (14%), EDSS 6 (14%), EDSS 7-9 (0%). We assumed persons to be treatment naïve (i.e. no previous experience with a DMT).

Intervention and comparator

The Optoferon therapy consists of a bioelectronic cell-based implant that allows for controlled release of INF-β 1a into the body (235). The Optoferon therapy involves INF-β 1a, secreted by optogenetically programmed mammalian cells. Because it is produced by mammalian cells, the active principle is most similar to the molecular composition of INF-β 1a of Avonex. The comparator, therefore, was intramuscular injectable Avonex (dosage 30 micrograms 1x per week). Given that no clinical trial has yet taken place to determine the efficacy and side effect profile of Optoferon, results found in the pivotal trials of Avonex were used to populate the model and adapted where deemed necessary.

The differences in the treatment pathway of Optoferon and Avonex are visualized in Figure 1. The treatment pathway for Avonex follows the Dutch treatment guidelines for first-line therapy in the Netherlands (236). The treatment pathway for Optoferon was based on a group discussion with two MS specialists who are members of the Optogenerapy consortium and three independent clinical experts on MS. The device, roughly 6 cm x 2 cm x 0.5 cm, will be placed by a general surgeon underneath the skin in the lower back. A specific insertion toolkit has been developed that allows for a minimally invasive procedure, such that implantation can be performed in a daycare setting without the need for the hospital admission. It is assumed that the bioelectronic implanted device would operate in the body for up to three years, thereafter the device will have to be replaced in year 4 and year 7. The replacement of device would follow the same procedure as implantation.

Figure 1a Treatment pathway for injectable INF-β 1a

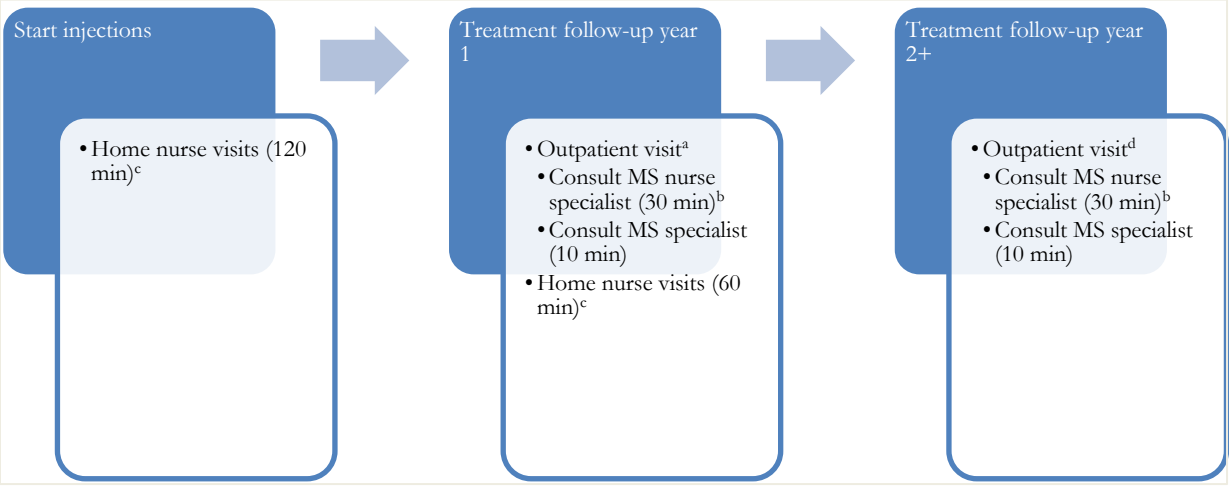
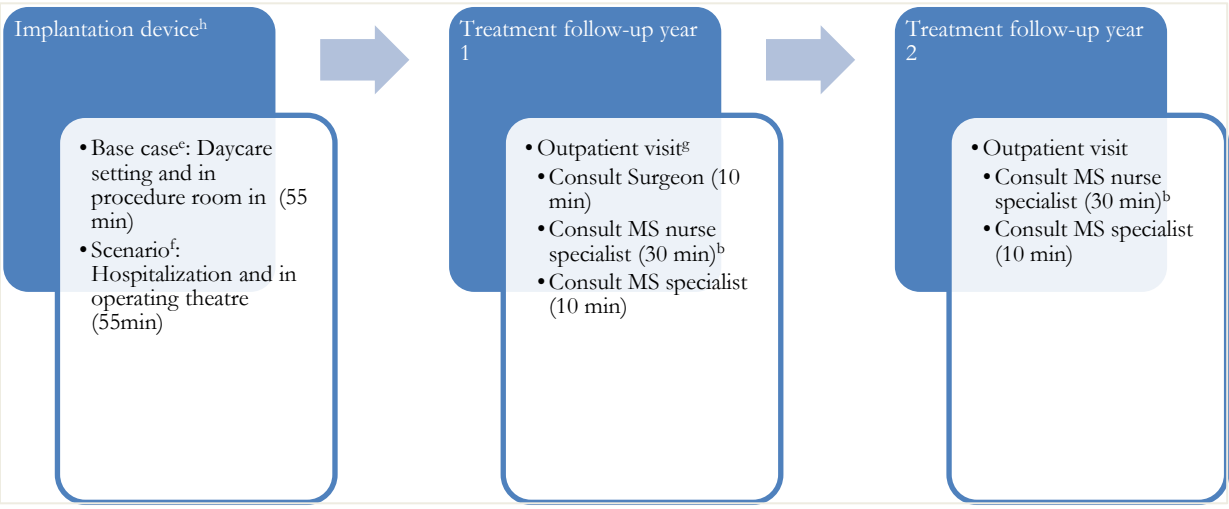


Figure 1b Treatment pathway for Optoferon



INF-β 1a: beta interferon, min: minutes, MS: multiple sclerosis. [a]This visit is planned 3 months after the start of injectable INF-β 1a, [b]Blood pressure measurement and laboratory tests done, including: thrombocytes, leukocytes, creatinine, alanine aminotransferase, lactate dehydrogenase, gamma-glutamyl transpeptidase, thyroid stimulating hormone, [c]The home nurse comes to explain how to inject and answer any queries regarding the treatment course, [d]For follow-up beyond, and including year two, the consult at the outpatient clinic is once per year, [e]In the base case analysis the implantation is done in a procedure room in a day-care setting, the costs include procedure-related costs (surgeon, nurse, medication, materials), room-related costs (materials and cleaning) and overhead costs, [f]In the scenario analysis the implantation is done in an operating theatre and the patient is hospitalized for one night, the costs include procedure-related costs (surgeon, nurse, medication, materials), room-related costs (materials and cleaning) and overhead costs, [g]Post-operative monitoring includes a consult with the surgeon 7 days post-implantation. The consult with the MS nurse specialist and MS specialist occurs 3 months post-implantation, [h]Implantation is performed in year 1, 4 and 7, therefore, if a patient remains on treatment, costs for removal and re-implantation occur in year 4 and 7.

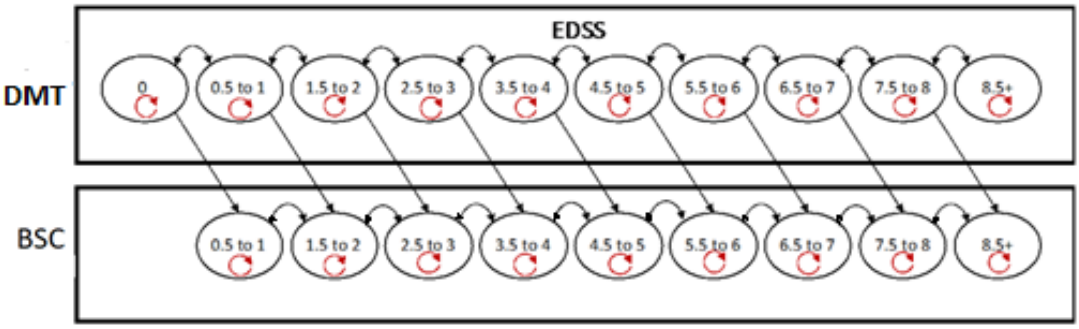
Model overview and inputs

A Markov model was developed in Microsoft Excel and adapted from a model previously developed (Figure 2) (237–239). The adaptation involved the assumption that persons transition to best supportive care (BSC) rather than to secondary progressive MS (SPMS). The cost-effectiveness of Optoferon was modelled with a 1-year cycle and estimated disease progression through eleven health states. RRMS patients progressed within EDSS 0-9, once they withdraw from treatment patients transition to BSC and continue progression within EDSS 0-9 and death. In each cycle, patients could remain in the same disease state, progress to a higher or lower disease state (disability could worsen or improve), could have a relapse, or withdraw from treatment and continue with BSC. The model did not take into account progression to secondary progressive MS (SPMS) or switching to a second-line DMT. Patients that withdraw from treatment could remain in the same disease state, progress to a higher or lower disease state or have a relapse. Furthermore, it was assumed that patients that reach EDSS 7 or higher stop treatment and switch to BSC.

In accordance to the Dutch economic guidelines, a societal perspective was taken (133). However, we chose to deviate from a lifetime horizon, as suggested by the Dutch guidelines, and model a time horizon of 9 years. The consortium assumes the device can be implanted in the body for a maximum of three years and then needs replacement. Additionally, the consortium did not find it feasible to implant the device more than 3 times per person because of the potential risk of scar tissue formation with reimplantation potentially reducing the efficacy of the implant. A half-cycle correction was performed.

The consolidated health economic evaluation reporting standard (CHEERS) checklist was used (240) and the Assessment of the Validation Status of Health-Economic (AdViSHE) tool was used to guide model validation (241). Model validity is warranted because we use a model that is commonly used to assess cost-effectiveness of MS treatments (237–239), the input parameters have been assessed at consortium meetings, and cross validation testing will be performed to compare the outcomes to models that address similar problems.

Figure 2 The Markov model



The model has been adapted from the Institute for Clinical and Economic Review report (ICER report) (237). BSC: best supportive care, DMT: disease-modifying therapy (patients receive either Optoferon or Avonex), EDSS: expanded disability status scale, black arrow: transition from EDSS state, red arrow: relapse.

Costs

The costs included in the analysis were based on the expected Dutch treatment pathway of Optoferon and current treatment pathway of Avonex (236) (Figure 1). Types of costs were based on the Dutch pharmacoeconomic guidelines (133) (Table 1). As such, multiple cost categories were identified: direct health care costs, direct non-health care costs and indirect non-health care costs. Although the Dutch guidelines advise to include indirect medical costs (i.e. all medical costs incurred due to life years gained) (133), these were excluded in the analysis since Optoferon was not expected to lead to a substantial life expectancy gain versus Avonex. Costs were reported in 2019 Euros (costs were corrected using the consumer price index when necessary) and were discounted at a 4% annual rate (133).

The acquisition costs for Optoferon were set equal to the acquisition costs for Avonex. The Optoferon device was developed using high volume manufacturing techniques which allow for mass fabrication and readily available Optoferon devices to enter the market at a competitive cost (i.e. the production line is already intact, therefore no investments are needed) (29,234). Therefore, we do not believe the costs will be higher than the costs for Avonex. The acquisition cost for Avonex was calculated by multiplying the unit costs and treatment regimen. The unit costs for Avonex in the Netherlands were sourced from www.medicijnkosten.nl (accessed on 7-1-2020). Administration costs, monitoring costs, adverse events costs and indirect health care costs (productivity loss due to treatment administration) were based on the Dutch Costing Manual (2015), consultation with clinical experts, www.farmacotherapeutischkompas.nl (accessed on 5-11-2019), and www.shl-groep.nl (accessed on 14-11-2019). Implantation costs were derived from Kanters et al. (2016) since the procedure is somewhat similar, though in a different location (242). Disease costs per disability state in the model were mainly obtained from the Dutch burden and cost study by Uitdehaag et al. (2017). To approximate the annual cost caused by relapses, the cost was calculated as the difference in costs between patients with and without a relapse over a three-month period and converted to yearly costs (243).

Table 1 Model inputs at baseline

Model inputs	Optoferon	Avonex	Standard Error	Distribution	Lower bound	Upper bound	Reference
Costs							
Treatment costs							
Acquisition costs [a]	€ 12,028	€ 12,028	€ 3,608	Gamma [g]	6029	20063	(244,245)
Administration costs [b]	P: € 185 H: € 1,026	€ 156	O_P: € 56 O_H: € 308 A: € 47	Gamma	O_P: 93 O_H: 514 A: 78	O_P: 310 O_H: 1711 A: 260	(40,242) [, c]
Removal device	P: € 277 H: € 1,210	NA	P: € 83 H: € 363	Gamma	P: 139 H: 606	P: 463 H: 2018	(40,242) [, c]
Monitoring costs [d]							
Year 1	€ 82	€ 218	O: € 25 A: € 65	Gamma	O: 41 A: 110	O: 137 A: 363	(40,246) [, c]
Year 2	€ 62	€ 140	O: € 19 A: € 42	Gamma	O: 31 A: 70	O: 103 A: 233	(40,246) [, c]
Year 3	€ 62	€ 62	O: € 19 A: € 42	Gamma	O: 31 A: 70	O: 103 A: 233	(40,246) [, c]
Indirect costs [e]							
Year 1	€ 115	€ 58	O: € 35 A: € 18	Gamma	O: 58 A: 29	O: 192 A: 96	(40)
Year 2	€ 12	€ 23	O: € 3 A: € 7	Gamma	O: 6 A: 12	O: 19 A: 38	(40)
Year 3	€ 12	€ 12	O: € 3 A: € 3	Gamma	O: 6 A: 6	O: 19 A: 19	(40)
Natural history costs							
Direct medical cost							
EDSS 0 – 3	€ 4,140	Equal	€ 1,242	Gamma	2075	6907	(243)
EDSS 4 – 6	€ 8,127	Equal	€ 2,438	Gamma	4074	13557	(243)
EDSS 7-9	€ 10,264	Equal	€ 3,079	Gamma	5145	17121	(243)
Other direct costs							
EDSS 0 – 3	€ 705	Equal	€ 211	Gamma	353	1176	(243)
EDSS 4 – 6	€ 2,055	Equal	€ 617	Gamma	1030	3429	(243)
EDSS 7 – 9	€ 2,080	Equal	€ 624	Gamma	1043	3470	(243)
Indirect medical costs							
EDSS 0 – 3	€ 161	Equal	€ 48	Gamma	81	269	(243)
EDSS 4 – 6	€ 33	Equal	€ 10	Gamma	16	55	(243)
EDSS 7 – 9	€ 21	Equal	€ 6	Gamma	11	35	(243)
Informal care costs							

EDSS 0 – 3	€ 803	Equal	€ 241	Gamma	403	1340	(243)
EDSS 4 – 6	€ 3,461	Equal	€ 1,038	Gamma	1735	5773	(243)
EDSS 7 – 9	€ 6,201	Equal	€ 1,860	Gamma	3108	10344	(243)
Relapse costs	€ 12,622	Equal	€ 3,787	Gamma	6327	21056	(243)
Utilities							
Baseline health utility							
EDSS 0	0.93	Equal	0.28	Beta	0.22	1	(243)
EDSS 1	0.86	Equal	0.26	Beta	0.25	1	(243)
EDSS 2	0.78	Equal	0.24	Beta	0.27	1	(243)
EDSS 3	0.67	Equal	0.21	Beta	0.27	0.96	(243)
EDSS 4	0.70	Equal	0.20	Beta	0.27	0.97	(243)
EDSS 5	0.69	Equal	0.20	Beta	0.27	0.97	(243)
EDSS 6	0.65	Equal	0.20	Beta	0.27	0.94	(243)
EDSS 7	0.53	Equal	0.16	Beta	0.23	0.81	(243)
EDSS 8	0.36	Equal	0.11	Beta	0.17	0.58	(243)
EDSS 9	0.04	Equal	0.01	Beta	0.02	0.07	(243)
Disutility							
Relapse	-0.07	Equal	0.02	Beta	0.04	0.12	(247)
SSI, superficial	-0.03	NA	0.01	Beta	0.01	0.05	(248)
SSI deep	-0.16	NA	0.05	Beta	0.08	0.26	(248)
Flu-like symptoms	-0.20	Equal	0.06	Beta	0.10	0.33	(249)
Headache	-0.03	Equal	0.01	Beta	0.01	0.05	(250)
Myalgia / muscle pain	-0.03	Equal	0.01	Beta	0.01	0.05	
Depression	-0.45	Equal	0.14	Beta	0.21	0.71	(249)
Fatigue	-0.06	Equal	0.02	Beta	0.03	0.10	(251)
Fever	-0.05	Equal	0.01	Beta	0.02	0.08	
Injection site reaction	NA	-0.01	0.003	Beta	0.01	0.02	(252)
Accidental injury injecting	NA	-0.03	0.01	Beta	0.01	0.05	(250)
Carer disutility							
EDSS 0 - 3	-0.002	Equal	0.001	Beta	0.001	0.003	(253)
EDSS 4	-0.05	Equal	0.01	Beta	0.02	0.08	(253)
EDSS 5	-0.14	Equal	0.04	Beta	0.07	0.23	(253)
EDSS 6	-0.16	Equal	0.05	Beta	0.08	0.26	(253)
EDSS 7	-0.17	Equal	0.05	Beta	0.08	0.28	(253)
EDSS 8	-0.03	Equal	0.01	Beta	0.01	0.05	(253)
EDSS 9	-0.10	Equal	0.03	Beta	0.05	0.16	(253)
Transition probabilities							
Efficacy							
Disability progression (HR)	0.79	Equal	0.12	Lognormal	0.63	1	(237)
Annual relapse rate	0.66	0.83	O: 0.13 A: 0.06	Lognormal	O: 0.57 A: 0.73	O: 0.74 A: 0.94	(113,237,254)

Relapse rate leading to hospitalization	0.79	Equal	0.23	Lognormal			(255)
Withdrawal treatment							
Annual withdrawal rate	2.7%	5.3%	NA	Beta	O: 0.02 A: 0.04	O: 0.04 A: 0.07	(237,256,257)
Adverse events (probability)							
SSI, superficial	0.22%	NA	NA	Beta	0.05%	0.54%	(258)
SSI, deep	0.22%	NA	NA	Beta	0.05%	0.54%	(258)
Flu-like symptoms [f]	50%	55%	NA	Beta	O: 48% A: 54%	O: 51% A: 57%	(259–261)
Headache	24%	Equal	NA	Beta	23%	26%	(261)
Myalgia / muscle pain	14%	Equal	NA	Beta	13%	16%	(261)
Depression	14%	Equal	NA	Beta	13%	15%	(261)
Fatigue	11%	Equal	NA	Beta	10%	12%	(261)
Fever	7%	Equal	NA	Beta	6%	8%	(261)
Injection site reaction	NA	12%	NA	Beta	11%	13%	(261)
Accidental injury injecting	NA	7%	NA	Beta	7%	8%	(261)

A: Avonex, Equal: equal costs for Optoferon and Avonex, H: hospital stay, HR: hazard ratio, NA: not applicable, O: Optoferon, P: procedure room, SE: standard error, SSI: surgical site infection. [a] The acquisition costs for Optoferon are incurred when the device is implanted (i.e. year 1, year 4, year 7, etc.). The acquisition costs for Avonex are annual. [b] The administration costs for Optoferon are incurred when the device is implanted (i.e. year 1, year 4, year 7, etc.). The administration costs for Avonex are incurred only in year 1. [c] Clinical experts. [d] The monitoring costs for Optoferon are cyclical, costs year 1 = year 4, year 2 = year 5, year 3 = year 6, etc. The monitoring costs for Avonex are constant after year 3. [e] The indirect costs for Optoferon are cyclical, costs year 1 = year 4, year 2 = year 5, year 3 = year 6, etc. [f] Differences in probabilities are due to the assumption that the lower dosage of Optoferon will lead to less flu-like symptoms (259,260). [g] This distribution is only applicable to Avonex.

Utilities

The baseline health utilities for patients with RRMS were obtained from Uitdehaag et al. (2017) (243). A single disutility value due to relapse, and independent from EDSS state, was set at -0.071 (247). Equal disutility values were used for common adverse events from Optoferon and Avonex. Two additional adverse events specific to Optoferon were included: superficial post-operative wound infection (defined as a surgical site infection (SSI) not requiring surgery treated with oral antibiotics) and deep wound infection (SSI requiring removal of the device and oral antibiotics). Two adverse events specific to injectable DMT were included: injection site reactions and accidental injury caused by injection. The QOL of informal carers for patients with MS was included as disutility (253). Healthcare effects were discounted at a 1.5% annual rate (133).

Transition probabilities

Equal disability progression and relapse rate leading to hospitalization values were used for Optoferon and Avonex.

Non-adherence of injectable DMTs reduces the effect they have on the risk of relapse rate (113,233). We calculated a 21% reduced risk of relapse for persons with Optoferon because we assume 100% adherence to Optoferon (since the device will continuously release the drug into the body, thereby avoiding the need for self-administration) and <80% adherence to Avonex because a systematic review found adherence rates between 63-75% for persons with RRMS taking first-line injectable DMT (186). Furthermore, the retrospective claims database study by Tan et al. (2011) demonstrated a 21% lower risk of relapse for persons >80% adherent to first-line injectable (113). As such, the annualized relapse rate (ARR) of Optoferon is derived and dependent on the ARR of Avonex presented in the Institute for Clinical and Economic Review Report (ICER Report), and we assumed an ARR of 0.66 vs 0.83, respectively (237).

Since the withdrawal rate of Optoferon is unknown, we assumed that the discontinuation rates would be comparable to rates found among diabetes patients treated with an insulin pump. This is because the treatment mechanism of the insulin pump is similar to that of Optoferon and because the reasons for discontinuation are mostly driven by adverse events. We assumed that patients receiving Optoferon are 50% less likely to withdraw from treatment compared to those taking Avonex (2.65% vs. 5.3%, respectively) based on reported discontinuation rates of Avonex and the discontinuation rates amongst diabetes patients treated with an insulin pump (1% for adults up to 4% among adolescents) (237,256,257).

The natural history disease progression transition probabilities for RRMS (with and without treatment) were based on the ICER Report on DMT effectiveness (Appendix 1) (237). The transition probabilities combined data from the longitudinal London Ontario cohort data and two clinical trials (the DEFINE and CONFIRM trial) (237).

The probability of adverse events was the same for Optoferon and Avonex, with the exception of flu-like symptoms. We assumed that the continued and more frequent release of INF-β 1-a into the body by the Optoferon device compared to the weekly injection of Avonex lead to a reduced probability of flu-like symptoms (259,260).

Base case, sensitivity and scenario analysis

Base case

Patients received the implant at the start of year 1 followed by replacement every 3 years thereafter (i.e. year 4, year 7). The costs of Optoferon were incurred at implantation. The model assumed that the acquisition costs of Avonex remained constant in consecutive years. The Dutch Healthcare

Institute considers three willingness-to-pay thresholds (WTP): €20,000/QALY (for treatments with a low disease severity), €50,000/QALY (medium disease severity), and €80,000/QALY (high disease severity) (262). Although the disease severity of RRMS can be considered high and the iMTA Disease Burden Calculator (iDBC) calculated a threshold of €80,000/QALY (263), we chose a more conservative approach and €50,000/QALY was considered the WTP threshold (264).

Sensitivity, scenario, and value of information analysis

To account for uncertainty in the model, we conducted deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA). An overview of all parameters used for the DSA and PSA is shown in Table 1. For the DSA, we changed relevant input parameters to values representing upper and lower bounds (at the 95% confidence interval values) of a pre-specified distribution. When no estimates about confidence intervals or standard error (SE) were available, the range of values were set at 30% of the base case value. In the PSA, 1000 Monte Carlo simulations were used to take into account parameter uncertainty by simultaneously varying model inputs given the annual acquisition cost of Optoferon (i.e. this parameter was not varied). The following distributions were used: gamma distribution for costs, beta distribution for probabilities and utilities, and a lognormal distribution for rates. Furthermore, we used the headroom method to assess the maximum additional costs of Optoferon over Avonex for Optoferon to still be deemed cost-effective using the WTP threshold of €50,000/QALY (265). We estimated the headroom per patient and per device unit (266).

Scenario analyses were performed to explore the effects of: 1) a higher acquisition cost of Optoferon (€20,000 and €50,000); 2) implanting Optoferon in an operation theater (thus requiring a one-night hospitalization) rather than in a procedure room; 3) yearly replacement of Optoferon, 4) no difference in withdrawal rate between Optoferon and Avonex, and 5) no difference in ARR between Optoferon and Avonex.

Value of information analysis was performed to examine whether it is worthwhile to invest more money to reduce decision uncertainty. We did so by estimating the expected value of perfect information (EVPI), which is the maximum amount a decision-maker should be willing to pay to eliminate decision uncertainty (40). Given the results of the PSA, the EVPI can be calculated as the average of the maximum net benefits across all PSA outcomes minus the maximum average net benefit for the different health technologies. Depending on the result of the EVPI (if the costs of the EVPI are higher than future costs of research), we may consider further analyses such as the expected value of partial perfect information (EVPPI) to examine the contribution of individual parameters to the overall decision uncertainty (40).

RESULTS

Base case

An overview of the base case results is given in Table 2. Optoferon dominated because it led to cost reductions (-€ 26,966) and health gain (0.45 QALYs gained). The main driver behind the cost reduction was the acquisition cost, with acquisition cost for Optoferon being two-and-a-half times less compared to the cost for Avonex (an incremental cost difference of -€ 47,333). Furthermore, Optoferon led to fewer adverse events costs and monitoring costs. However, its administration costs, indirect treatment costs and total disease costs were higher compared to Avonex (incremental cost differences of €752, €217, and €15,355, respectively). The higher total disease costs for Optoferon are due to the slight increase in life years. The cumulative total cost per patient over time is presented in Figure 3a.

The lower withdrawal rate from Optoferon to BSC, compared to Avonex, led to more patients remaining in a higher EDSS state resulting in an incremental QALY gain of 0.45 for patients receiving Optoferon. Patients receiving Optoferon experienced slightly more adverse event disutility, and there were no differences in carer disutility and relapse disutility. The cumulative QALYs gained per patient is visualized in Figure 3b. Over the 9-year period, there was an incremental life-year gain of 0.63 for patients receiving Optoferon.

Table 2 Results from the base-case analysis

	Optoferon	**Avonex**	**Incremental Optoferon vs Avonex**
Total cost per patient	€ 153,621	€ 180,587	-€ 26,966
Treatment costs			
Total AE costs per year	€ 310	€ 330	-€ 19
Removal device costs	€ 483	€ 0	€ 483
Acquisition	€ 30,395	€ 77,729	-€ 47,333
Administration	€ 901	€ 149	€ 752
Monitoring	€ 498	€ 616	-€ 118
Indirect	€ 345	€ 128	€ 217
Total	€ 32,932	€ 78,951	-€ 46,019
Discounted costs	€ 29,639	€ 69,157	-€ 39,517
Disease cost			
Direct medical	€ 36,828	€ 32,919	€ 3,909
Indirect medical	€ 947	€ 845	€ 102
Other direct	€ 7,427	€ 6,643	€ 784
Informal care	€ 10,391	€ 9,300	€ 1,091
No hospital relapse	€ 39,566	€ 35,269	€ 4,297
Hospital relapse	€ 47,614	€ 42,443	€ 5,171
Total	€ 142,773	€ 127,418	€ 15,355
Discounted	€ 123,982	€ 111,431	€ 12,551
QALYs per patient			
EDSS utility	5.58	4.99	0.59
AE disutility	-1.22	-1.14	-0.09
Carer disutility	-0.03	-0.03	0.00
Relapse disutility	-0.02	-0.02	0.00
Total QALYs	4.30	3.80	0.50
Total QALYs discounted	3.82	3.37	0.45
Life years per patients			
Total LY	7.24	6.46	0.77
Total LY discounted	6.29	5.66	0.63
Incremental cost per QALY gained			-€ 60,255
Incremental cost per LY gained			-€ 42,612

AE: adverse events, EDSS: expanded disability status scale, LY: life years, QALYs: quality adjusted life years.

Figure 3a The cumulative costs per patient of Optoferon vs. Avonex

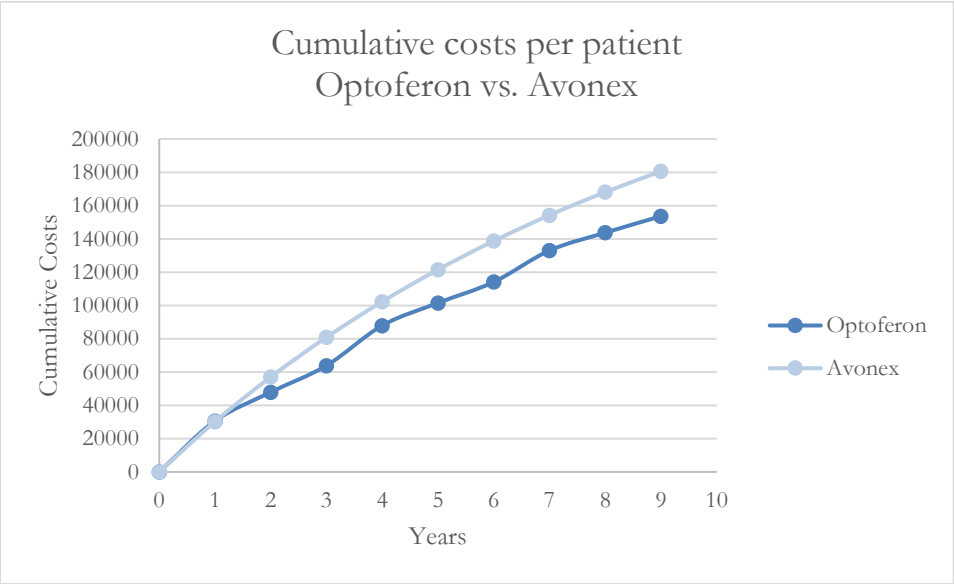
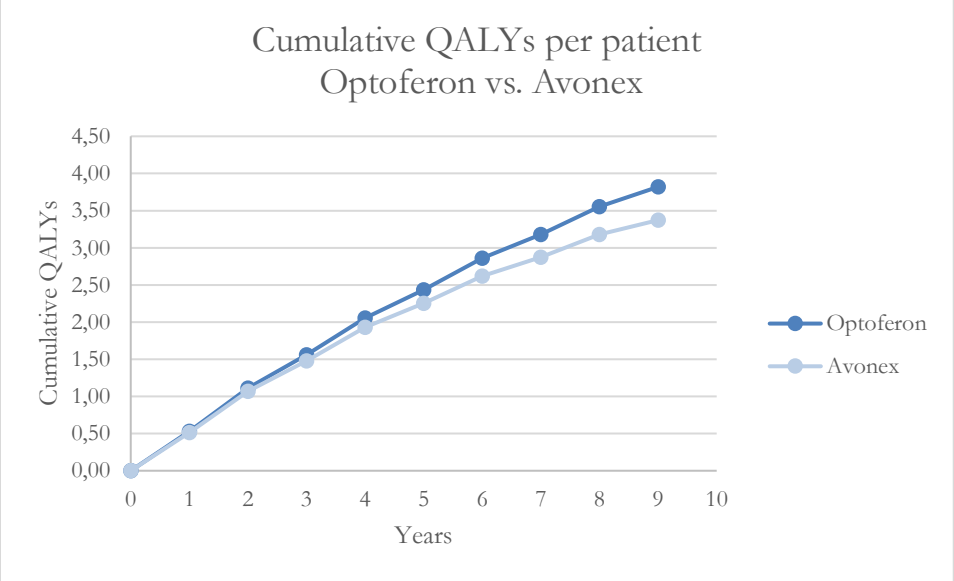


Figure 3b The quality adjusted life years (QALY) per patient of Optoferon vs. Avonex



QALYs: quality adjusted life years.

Sensitivity analysis

The 10 parameters that had the greatest impact on the ICER per QALY and LY are shown in Figures 4a and 4b. We find a range of possible ICERs based on the three main parameters identified with the deterministic sensitivity analysis. The ICER/QALY was most sensitive to variations in the annual acquisition costs of Avonex (range: -€ 161,824 to € 15,550), annual withdrawal rate of Avonex (range: -€ 161,064 to -€ 24,651), and annual withdrawal rate of Optoferon (range: -€ 129,561 to -€ 34,434). The ICER/LY was most sensitive to variations in the disability progression of Avonex (range: -€ 389,345 to € 378,399), annual acquisition cost of Avonex (range: -€ 114,443 to € 11,011), and annual withdrawal rate of Avonex (range: -€ 118,854 to -€ 17,156). Furthermore, EDSS 1-4 utility affects the ICER/QALY, whereas the ICER/LY was affected by hospital relapse costs and direct medical costs.

Optoferon remains dominant in all but one scenario. The lower bound of the 95% CI of the hazard ratio on disability progression of Avonex (improved effect Avonex compared to Optoferon), this led to higher negative incremental costs (total costs per patient for Avonex increases) and negative incremental QALYs (more QALY gain compared to Optoferon) which leads to a positive ICER of €39,470. Both annual acquisition costs and withdrawal rates for Avonex and Optoferon affect the ICER per QALY and per LY. Furthermore, the lower bound of the 95% CI of the hazard ratio on disability progression of Optoferon (improved effect of Optoferon compared to Avonex) leads to less negative incremental costs (total costs for Optoferon increase compared to Avonex) which leads an increase in LY gain, resulting in a less negative ICER/LY (-€ 7,766).

Figure 5 shows the cost-effectiveness plane visualizing the uncertainty around the cost-effectiveness outcomes. Most of the estimates lie within the southeast quadrant (health gains and lower costs) or northeast quadrant (health gains and higher costs). Figure 6 shows the cost-effectiveness acceptability curve for Optoferon and Avonex. If a WTP threshold of €50,000/QALY is used, there is a probability of cost-effectiveness for Optoferon of 99.6%.

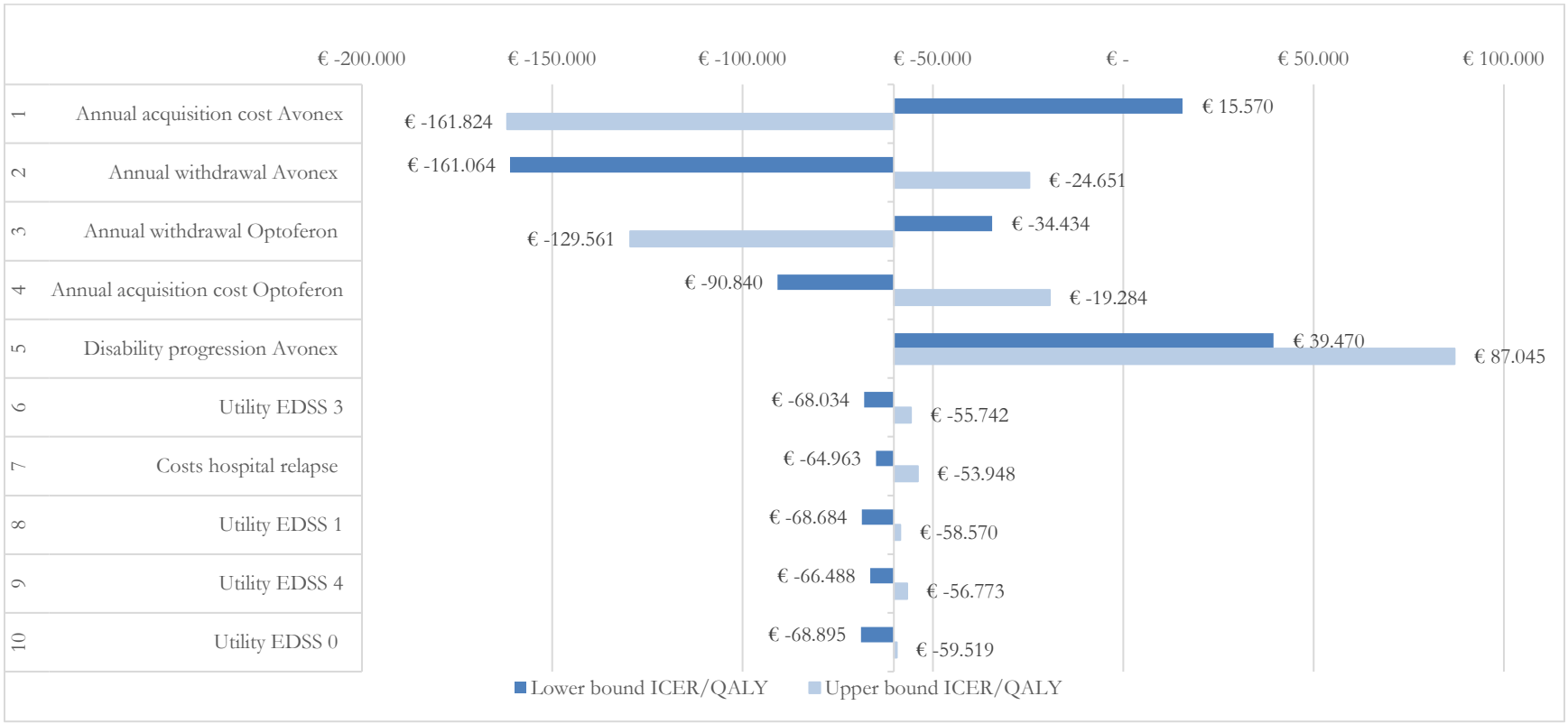
Headroom

Table 3 shows the maximum additional costs of Optoferon over Avonex for Optoferon that are possible to ensure that Optoferon can be still deemed cost-effective based on a WTP threshold of €50,000/QALY. Taking into account cost savings and assuming the potential cost-savings will be fully recouped by the manufacturer in the sales product price, the headroom per patient was (€50,000 * 0.45) + €26,966 = €49,343. As expected, the headroom decreases as acquisition costs increase; if the acquisition costs were €50,000, Optoferon is no longer cost-saving versus Avonex.

Scenario and value of information analysis

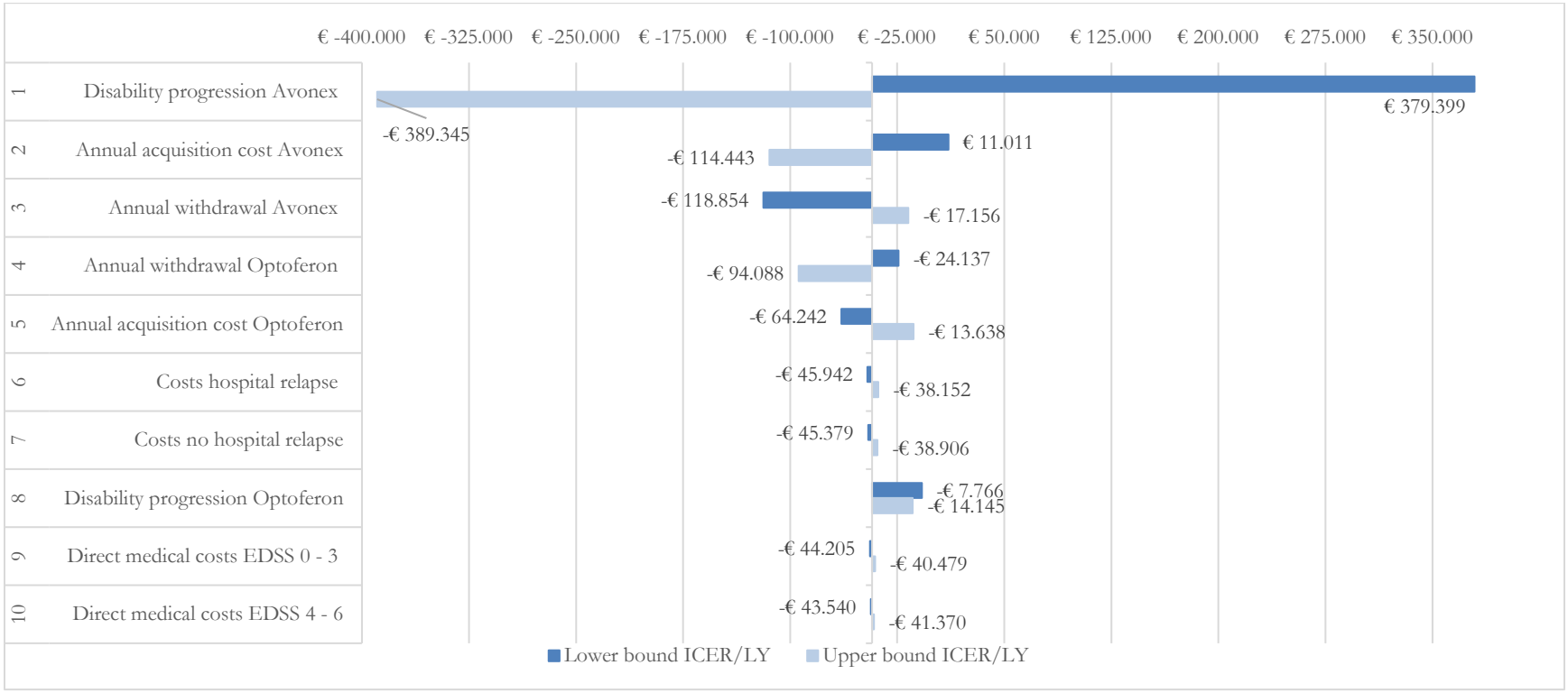
The scenario analyses showed that Optoferon remains the dominant strategy in four scenarios (Optoferon acquisition costs of €20,000; hospitalizing the patient for the implantation and removal the device; setting withdrawal rates of treatment equal; and setting ARR of treatment equal) (Table 4). Optoferon was no longer a cost-effective strategy when increasing the acquisition costs to €50,000 (with higher costs and QALYs gained). Optoferon remained a cost-effective strategy if the implant would be implanted and replaced yearly. The estimated EVPI per person is equal to €13.60. Given than the EVPI is less than costs of future research, we refrained from estimating the EVPPI.

Figure 4a Tornado diagram to show the impact of uncertainty of model parameters on the model outcomes per quality adjusted life year



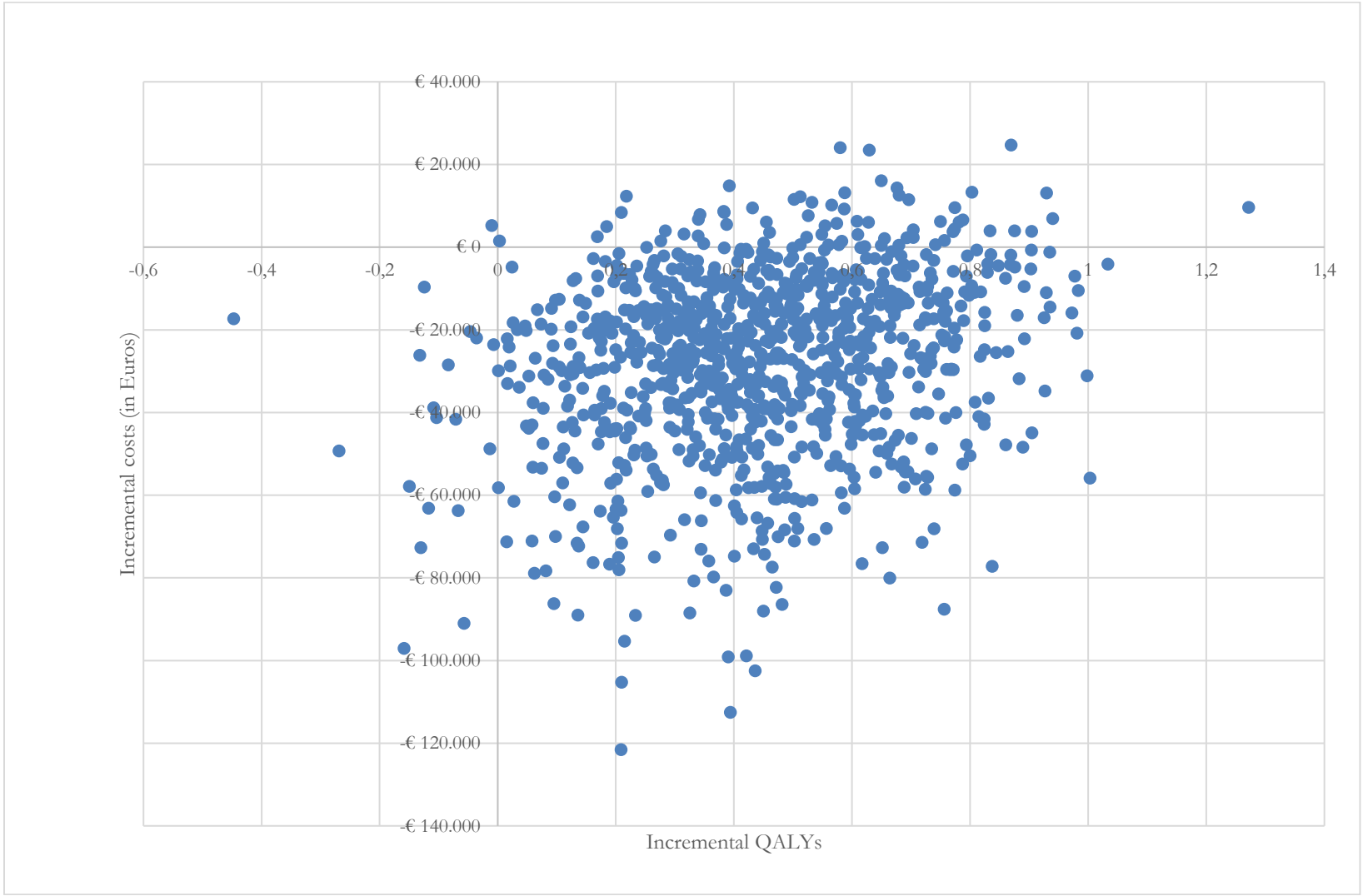
EDSS: expanded disability status scale, ICER: incremental cost effectiveness ratio, QALY: quality-adjusted life year.

Figure 4b Tornado diagram to show the impact of uncertainty of model parameters on the model outcomes per life year (LY)



EDSS: expanded disability status scale, ICER: incremental cost effectiveness ratio, LY: life year.

Figure 5 The cost-effectives plane of Optoferon vs. Avonex



QALYs: Quality adjusted life years.

Figure 6 Cost-effectiveness acceptability curve of Optoferon vs. Avonex

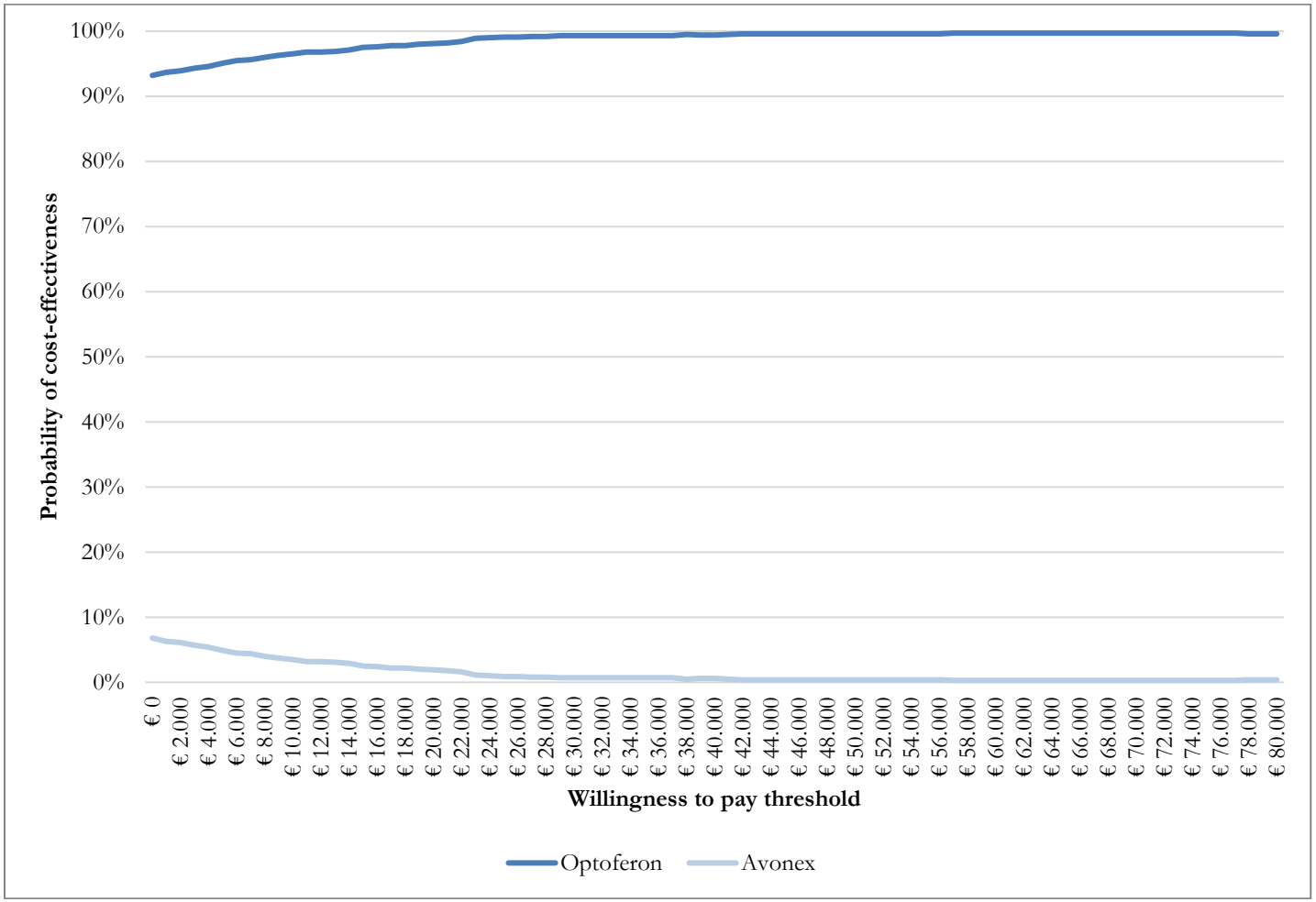


Table 3 Results from the headroom analysis

	Δ QALYs	Δ Cost	Headroom per patient	Headroom per device unit [a]
Optoferon acquisition cost: €12,028	0.45	-€ 26,966	€ 49,343	€ 49,343
Optoferon acquisition cost: €20,000	0.45	-€ 8,775	€ 31,153	€ 31,153
Optoferon acquisition cost: €50,000	0.45	€ 59,678	-€ 37,301	-€ 37,301

QALYs: quality adjusted life years, Δ difference in. [a] N=1 patient per device unit.

Table 4 Results from the scenario analyses

	Total cost per patient	Incremental costs (Optoferon vs Avonex)	Incremental QALYs	Incremental LY	ICER/QALY	ICER/LY
Base case	€ 153,621	-€ 26,966	0.45	0.63	-€ 60,255	-€ 42,612
Optoferon acquisition cost: €20,000	€ 171,812	-€ 8,775	0.45	0.63	-€ 19,607	-€ 13,866
Optoferon acquisition cost: €50,000	€ 240,265	€ 59.678	0.45	0.63	€ 133,348	€ 94,305
Hospitalization patient for the implantation and removal device	€ 156,764	-€ 23,823	0.45	0.63	-€ 53,232	-€ 37,646
Optoferon implanted and replaced yearly	€ 203.948	€ 23,361	0.45	0.63	€ 52,200	€ 36,916
Optoferon withdrawal rate set equal to Avonex	€ 138,968	-€ 41,619	0.02	0	-€ 2,552,470	NA
Optoferon ARR set equal to Avonex	€ 153.621	-€ 26.966	0.44	0.63	-€ 60,741	-€ 42,612

ARR: annualized relapse rate, ICER: incremental cost-effectiveness ratio, LY: life year, NA: not applicable, QALY: quality adjusted life year.

DISCUSSION

We performed an early cost-effectiveness analysis (CEA) of a potentially disruptive innovation in the field of drug delivery for MS patients. This early CEA finds that the novel mode of implantable combined ATMP DMT administration, Optoferon, for patients with RRMS is a dominant strategy when compared to the injectable administration of Avonex. Use of the Optoferon therapeutic strategy has the potential to reduce costs and improve health outcomes as long as it fulfils expectations regarding safety, effectiveness and acquisition costs.

This study shows that there is a potential market for a bioelectronic implantable cell-based device within the field of MS. Though we only examined the possibility of an implantable device with INF-β 1a delivery, the device described here can be used to administer other DMTs. More efficacious first- and second-line DMTs reduce relapse rate, slow down disease progression (162), improve work productivity (267), and can be cost-effective compared to INF-β 1a in both Europe and the USA (41). As therapeutic antibodies are difficult to manufacture and always require injections (with drawbacks such as injection-related side effects), there is a growing need for an alternative delivery route like an in-situ controlled drug delivery using an implantable cell-based device (27).

The bioelectronic device can be used in a wide variety of diseases to potentially improve health outcomes and healthcare efficiency. The constantly growing portfolio of therapeutic antibodies offers many new therapeutic avenues to treat chronic diseases, including several forms of cancer. Implantable cell-based biologic delivery devices are currently being tested for the treatment of diabetes (268), ophthalmic disease (269) and neurodegenerative conditions (270). In principle, the cell therapy vehicle can be genetically programmed to secrete other therapeutic proteins, cytokines or even efficacious DMT antibodies like natalizumab and alemtuzumab.

Headroom analysis may help the industry to position the product on the market (31). However, it may be questionable whether the whole headroom should be utilized. There might be reasons to position the product at a lower price and focus on value generated rather than revenue. The value of new technology for innovation policy is driven by the potential business opportunities it may create, whereas in health policy, the emphasis should be on health gains to society (271). There are widespread inequalities regarding the access to MS care across Europe (44). This is caused by different regional pricing and HTA processes in which CE, the burden of the disease, quality of evidence and the healthcare budget of countries determine the access to care (44). Along with differing market access strategies from the industry. However, all stakeholders involved in MS care should have a say in how scarce resources are allocated. While the use of stakeholder preferences in HTA decisions may cause problems due to the heterogenous results of preferences, the use of generic QOL measures, such as the EQ-5D enables conformity across HTA decisions (272). However, it remains important to examine closely the added value a product has to the patient and then market according to that.

We had to make assumptions regarding adherence, withdrawal, and relapse rates. However, we found comparable results to a similar cost-effectiveness analysis of first-line DMTs (peginterferon beta vs INF-β 1a) performed by Hernandez et al (2016). The same conceptual model is used, along with a short time horizon (10 year horizon), and the results are most sensitive to variations of the treatment effect on disability progression and acquisition costs (239).

We estimated the EVPI to be €13.60 per person, however this is based on an economic evaluation performed in the Netherlands, and more information is needed to reduce decision uncertainty. Therefore, more research is needed to obtain a better estimate of the cost-effectiveness of Optoferon. A multi-country RCT with a follow-up of at least three years is needed to establish the efficacy and safety of the device, along with the gathering of all relevant data needed for CEAs such as (in)direct (non-)health care costs. Such cost categories can be collected at certain follow-up

moments and we recommend the use of the iMTA Productivity Cost Questionnaire and the iMTA Medical Consumption Questionnaire (273,274). RCT results can replace the important assumptions that we used in this model and a head-to-head trial is strongly recommended over combining efficacy data from individual trials (different study designs, populations, and outcome measures) (275). Furthermore, the RCT data can be used to refine the model, for example by using shorter model cycles.

Early economic evaluations inform manufacturers whether it is advisable to continue developing a medical technology (a go/no-go recommendation). Even though medical innovation development is mostly paid by public and private investors and not directly by patients and physicians, a more holistic view should be adopted when deciding on the continuation of technological advancements. Techniques such as multiple criteria decision analysis (MCDA) and discrete choice experiments (DCEs) can elicit patient and stakeholder preferences to help establish the societal value of the product (31). Furthermore, the preferences can be incorporated during technology development (205) and there is consensus from the industry, regulatory authorities and HTA bodies to do so (182). Thus, we encourage future go/no-go recommendations to also include patient elicitation methods and not just clinical and economic factors, such as cost-effectiveness.

This study has some limitations. This study has some limitations. Firstly, the main assumption of this model is based on the premise that Optoferon can improve adherence and thereby ARR. However, ARR does not really affect QALYs, which means that it is not one of the top 10 parameters affecting the ICER. What does have a profound effect on the ICER/QALY and ICER/LY is the disability progression of Avonex and Optoferon, respectively. Slower disability progression (i.e. less progression) means that persons will be less disabled for a longer period of time, resulting in increased QALYs and LYs. Such results have also been found in a comparable economic evaluation by Hernandez et al (2016). Secondly, we did not examine other first-line DMTs, for example oral dimethyl fumarate, resulting in a limited comparison of the current first-line treatment landscape. Oral DMTs have been found to be cost-effective compared to INF-β 1a (238,276–278). Oral DMTs need to be considered as comparators to Optoferon in future clinical trials and economic evaluations because national HTA agencies will probably consider this in their decision-making process. Thirdly, we used a 9-year time horizon instead of the lifetime time horizon recommended in the Dutch economic guideline (133). However, based on our findings, a longer time horizon would have only increased the expected cost-savings and health gain from using Optoferon (see Figure 3). Fourthly, indirect future medical costs were not incorporated in our analysis. Since we estimated a gain in life expectancy of 0.69 years from Optoferon, inclusion of indirect costs would have reduced the cost-effectiveness of Optoferon. Finally, the model did not include SPMS patients or the ability to switch to another DMT, thus not reflecting clinical practice and limiting the generalizability of the results. We agree with and repeat the advice given by Hernandez et al. (2018), that future economic models should model sequential treatment courses (275). Ideally, the development of the device could incorporate such needs, thus Optoferon initially releases first-line DMT into the body, and when deemed necessary, switch the cells to release a 2nd-line DMT and model that accordingly.

CONCLUSION

This early CEA suggests that innovative cell-based bioelectronic implant technology within the field of MS can reduce costs and have positive health effects. In light of all the uncertainties presented in this economic evaluation, Optoferon may be a cost-effective solution and has the potential to become a new mode of treatment administration for patients with MS. The cell therapy vehicle may also become a mode of administration for second-line therapy for MS patients, or for treatments in other

disease areas, because genetically programming the cells to secrete other therapeutic proteins is, in principle, possible. It is important to determine the added value of the product to the patient and the market, therefore trial data and stakeholder preferences are needed.

APPENDIX

Appendix 1a The natural history disease progression transition probabilities based on the London Ontario set

	EDSS state end of the year									
EDSS state at the beginning of the year	0	1	2	3	4	5	6	7	8	9
0	0.312	0.289	0.312	0.07	0.016	0.001	0	0	0	0
1	0.179	0.231	0.419	0.127	0.039	0.004	0.001	0	0	0
2	0.061	0.13	0.493	0.215	0.088	0.011	0.002	0	0	0
3	0.019	0.055	0.299	0.322	0.241	0.044	0.013	0.003	0.004	0
4	0.004	0.017	0.127	0.251	0.411	0.121	0.048	0.014	0.007	0
5	0.001	0.004	0.033	0.096	0.252	0.295	0.211	0.085	0.023	0
6	0	0.001	0.009	0.034	0.123	0.257	0.329	0.19	0.056	0.001
7	0	0	0.002	0.013	0.057	0.169	0.309	0.257	0.189	0.004
8	0	0	0	0	0	0	0	0	0.995	0.005
9	0	0	0	0	0	0	0	0	0	1

The natural history disease progression transition probabilities based on the London Ontario set (237)

Appendix 1b The natural history disease progression transition probabilities adapted with the Optoferon and Avonex disease progression hazard ratio

	EDSS state end of the year									
EDSS state at the beginning of the year	0	1	2	3	4	5	6	7	8	9
0	0.456	0.228	0.246	0.055	0.013	0.001	0.000	0.000	0.000	0.000
1	0.233	0.301	0.331	0.100	0.031	0.003	0.001	0.000	0.000	0.000
2	0.067	0.143	0.541	0.170	0.070	0.009	0.002	0.000	0.000	0.000
3	0.021	0.060	0.327	0.352	0.190	0.035	0.010	0.002	0.003	0.000
4	0.004	0.018	0.133	0.263	0.431	0.096	0.038	0.011	0.006	0.000
5	0.001	0.004	0.036	0.105	0.277	0.324	0.167	0.067	0.018	0.000
6	0.000	0.001	0.010	0.036	0.131	0.275	0.352	0.150	0.044	0.001
7	0.000	0.000	0.002	0.014	0.060	0.177	0.325	0.270	0.149	0.003
8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.996	0.004
9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000

The natural history disease progression transition probabilities adapted from the Institute for Clinical and Economic Review report (ICER report) on DMT effectiveness (237) with the Optoferon and Avonex disease progression hazard ratio (0.79 for both treatment options). EDSS: expanded disability status scale.

7
GENERAL DISCUSSION

While there is no cure for patients with multiple sclerosis (MS), there are many disease-modifying therapies (DMTs) that reduce disease progression and relapse rate. The three current modes of administration are injectables, pills, and infusion therapy, each with its specific efficacy and safety profiles. A novel mode of administration, a cell-based optogenetics drug delivery implant may enhance the treatment landscape. In this thesis, an early health technology assessment (HTA) was performed to assess the potential of this implant in MS care. In this chapter, the main findings are presented, implications of these results for stakeholders are assessed, lessons learnt, and future recommendations are given.

MAIN FINDINGS

The needs and preferences of persons with MS differ depending on the treatment decision-making moment, i.e. when to start, stop or switch disease-modifying therapy (DMT). All treatment decision-making moments are associated with uncertainty *(Chapter 4)*. By taking a DMT persons with MS perceive some control over the disease progression and this is a reason why they start or continue taking treatment *(Chapter 2 & 4)*. Patients are non-adherent to or stop taking a DMT because they forget to administer the treatment, suffer from side effects, and perceive a lack of efficacy. Moreover, patients switch therapy because of poor tolerability *(Chapter 2)*.

We performed a discrete choice experiment (DCE) to quantify the preferences and assessed trade-offs of persons with MS regarding three modes of administration: implant, pills, and injection therapy. Most of the respondents would choose the treatments described to them, however, preferences differed per type of MS, current DMT status, and mobility *(Chapter 5)*. Similar to the results of the studies included in the systematic review respondents preferred efficacious treatment *(Chapter 2 & 5)*. Interestingly, persons were willing to accept an increase in the risk of relapse rate or disease progression to switch their treatment administration from an injectable to an implantable device. Furthermore, the mean predicted uptake was highest for the implant, followed by pills, injections, and no treatment *(Chapter 5)*. The participants of the focus group sessions and respondents to the online survey also expressed an interest in the implant as a new mode of administration *(Chapter 4)*. However, persons with MS also still have doubts regarding the device and clinical evidence is needed before they would consider it as a mode of treatment administration *(Chapter 4)*.

Our health-related quality of life (HRQOL) survey amongst real-world MS patients from several European countries confirmed that persons with MS have low, and perhaps even lower than previously reported, HRQOL *(Chapter 3)*. Furthermore, we found cross-country differences in HRQOL and predictors of HRQOL are disability status and type of MS.

The Optogenerapy implant has the potential to be very cost-effective compared to injectable beta-interferon (INFβ). It can reduce healthcare costs (-€34,099) and improve health outcomes (0.49 quality-adjusted life years; QALYs gained) over a 9-year time horizon. Our findings suggest that implant therapy remains a dominant strategy in three scenarios: doubling the acquisition costs to €20,000, hospitalizing the patients one night for implantation (and removal of the device), and setting the withdrawal rates for the Optogenerapy implant and injectable therapy equal. Also, the Optogenerapy implant would remain cost-effective if the implant were to be implanted and replaced yearly *(Chapter 6)*. The headroom was calculated to be €58,557. These results hold as long as the implant fulfils expectations regarding safety, efficacy, and acquisition costs *(Chapter 6)*.

IMPLICATIONS OF THE RESULTS FOR STAKEHOLDERS

The drug delivery implant is an example of translational research: the transport of knowledge within a laboratory setting to a clinical application (179). The Optogenerapy consortium attempted to provide a bridge between the science of optoelectronics and cell-based drug delivery systems (i.e. optogenetics) to society by developing an implantable device for persons with MS. One could say that MS was a case study to determine whether it was possible to develop and demonstrate a wireless powered, cell-based, combined advanced therapy medicinal product (cATMP) that brings together various technologies into one implantable device (i.e. proof of principle study). Known concerns of translational research are whether the product will function as it was intended in the real world, or how to disseminate the new technology such that it becomes accessible for all persons to provide optimal healthcare (179,279)

In this discussion, we attempted to highlight implications of the results from this early HTA for the various stakeholder involved.

BOX 1: AN EXAMPLE OF WHY PATIENTS SHOULD BE INVOLVED IN PRODUCT DEVELOPMENT

Persons with MS are the end-user of the device and their views are necessary for optimal design. This was briefly explored in the focus group sessions, which were held later in the 3-year project; in hindsight, these should have been performed earlier. The sessions revealed to the consortium that the original location of the device in the body (the lower back) was not favoured by the patients. The participants mentioned that having an implant in the lower back may be painful when sitting against a chair, or might rub against clothing. Following that, the consortium debated whether the device should be implanted in the abdomen. Consequently, the surgical tools for implantation had to be redeveloped. But it also raised further questions such as, if we implant the device in the abdomen, will the wirelessly powered belt still be able to activate the implant?

MEDICAL TECHNOLOGY DEVELOPERS

Ideally, early HTA provides an essential understanding of the potential of new medical technology to the product developers. In our case, the product developers were the Optogenerapy consortium members, a public-private collaboration of 11 partners, of which most had a scientific background.

Was the consortium utilizing all relevant stakeholders?

To make the step from a theoretically working optogenetics drug delivery device to a clinical application that benefits the end-user of the device, the end-user (i.e. persons with MS) could have been the 12th partner in the consortium. Barriers of patient involvement in clinical decision-making are costs, scientists preferring to address topics that ensure them scientific acknowledgements (rather than topics deemed important by the patient), patients not having enough scientific know-how, and the assumption that patient involvement will delay scientific decision-making (280). Though it is unknown whether the above-mentioned reasons explain why the consortium did not have a patient organization as one of its partners, they might have been a welcome addition. Box 1 presents an example of why it could have been helpful to have a patient organization as a consortium member. For future projects we advise medical technology developers to involve patients in the research group.

A continuous dialogue initiated by the developers with the relevant stakeholders is desirable because a concern of translational research is that the product may not work as originally intended. Developers have to be aware that the DCE, focus group sessions, and the economic evaluation were based on assumptions regarding efficacy, safety, placement of the implant in the lower back of the body, and three-yearly implantations. The persons involved in the focus group sessions and the DCE were, in essence, hypothesizing on how the implant would fit into their daily lives. Having a medical device implanted may change how one perceives one's body and how one experiences their disease (175–178). End-user needs can guide product development and evaluation, and failure to include them may result in suboptimal commercial device success or discontinued use of the device by the persons with MS (281). An approach to elicit end-user needs are focus group and co-design sessions with the stakeholders (patients, product developers, healthcare professionals (HCP)) to discuss views and insights regarding the product development. However, such methods were not utilized during the Optogenerapy project. With that information, we could have made better-informed conclusions on the potential of the device. Whether the product will work as intended and how patients accept and incorporate it into their daily living can only be measured once the product is on the market. Presently it is not yet clear when this will be, therefore, until then we have to speculate.

It is important to have HCPs (physicians, nurses, social workers, physiotherapists) involved during the device development and HTA process because they are the key to the successful implementation of the device. Without the approval of the HCPs, medical technology (albeit drugs, devices, prevention programs) will not be routinely implemented in healthcare. Quantitative and qualitative tools can be used to elicit HCP preferences. For example, MCDA may help support (early) product development decisions and identify device-related preferences of HCPs (31,35). MCDA can also be used to quantify the value of aspects other than QOL-related issues (133), such as ease of use, monitoring, and organizational issues. Furthermore, in-depth interviews or focus group sessions with HCPs could have been appropriate to understand their views towards the Optogenerapy implant. It is the role of the medical technology developers to coordinate such activities. This is necessary such that not only device development is streamlined across stakeholders, but also because the qualitative and quantitative methods can be used as input for the HTA.

The potential, and the threat, of more efficacious treatments

The mean predicted uptake was the best for the implant (43%) compared to the other three modes of administration examined *(Chapter 5)*. The predicted uptake of the implant was based on the assumption that the safety and efficacy profiles of the implant were set equal to that of injectable INFβ. We find it plausible that if the genetically programmed cells are programmed to secrete other more efficacious therapeutic proteins, such as natalizumab or alemtuzumab, that the mean

predicted uptake would increase. This could potentially increase the market share of the Optogenerapy implant by making the device available for persons with secondary progressive and primary progressive MS. There is even the possibility of secreting therapeutic proteins for treating patients with other diseases, expanding the market possibilities even further.

However, a potential threat to the implant can be stem cell therapy for MS. Stem cell transplantation has the ability to reset and repair the immune system, rather than to suppress the immune system (282,283). Persons with severe treatment-resistant MS have been treated with autologous hematopoietic stem cell transplantation (aHSCT) for over 20 years, however, this is still not standard care in many European countries (283,284). The risk of treatment-related mortality has decreased substantially over the years, from 3.6% to 0.3% (studies before and after 2005, respectively) (285). This was deemed unacceptably high, resulting in reluctance to provide it as a treatment (283), and was a barrier to perform RCTs (285). For now, patients eligible for the implant and aHSCT are not similar (285,286), but this may change once more efficacious therapeutic proteins can be secreted by the implant. The cost-effectiveness of aHSCT is comparable to second-line DMTs, and may even be favorable over DMTs (282,284,286). Once aHSCT does become more widely accepted for active RRMS and progressive MS, the Optogenerapy implant may become somewhat redundant for that patient population. Therefore, performing SWOT (Strength, Weaknesses, Opportunities, and Threats) or PEST analyses (Political, Economic, Social, Technological) may be appropriate for strategic reasons (265).

What are some potential barriers for investors and how should these be overcome?

The next step is to make the Optogenerapy implant attractive for investors such as medical technology or pharmaceutical companies to finance the next phase of the product development: clinical research and market access. Public-private partnerships should in principle lead to research and development activities in which the societal needs (public health, economic growth, sustainability) are represented by the public partner, and the private partner knows the market and can make the right investments needed (287). The key is to share ideas, expertise, and accelerate the translation of science into new medical products, using a so-called open innovation approach (288). A private partner may be driven to make a profit through patenting for example. Thus, public-private partnerships may only work in health research if the private partner can make a return on investment (287). As such, medical technology developers should be aware of some potential barriers for investors.

The results from the early economic evaluation and headroom analysis of the Optogenerapy implant are promising, however concerns such as technological and market uncertainties should be addressed. For example, it is a challenge to determine the financial value of the implant because of technological uncertainties. No in-human trials have been performed, therefore the safety and efficacy of the implant have not yet been proven. Clinical research and randomised clinical trials (RCTs) are known to be costly for small-medium enterprises (289). However, this data is needed for market authorisation and must comply with EU legislation (290). Also, market uncertainties are present. The previously mentioned SWOT and PEST analyses are needed to know the competitive advantage of Optogenerapy, to explore whether the device is restricted to early RRMS patients, and to determine which country(s) are most suited for the initial launch. Finally, regulatory approval is not guaranteed. Therefore, choosing to invest in Optogenerapy relates to the financial risk investors are willing to make.

Additional concerns are related to the sometimes unavoidable limitations of early economic evaluations. The health economic model was based on assumptions that lead to model uncertainty (for example, the proposed treatment pathway) and input parameter uncertainty. Though the scenario and sensitivity analyses performed try to improve the interpretability of the outcomes, caution is always needed and the true cost-effectiveness cannot be calculated. To reduce some of that uncertainty, clinical trials have to be performed to collect data on safety, efficacy, quality of life status, and costs to better inform reimbursement decisions or market access and

pricing strategies. A financial investment is needed for such trials, but even then a certain amount of uncertainty surrounding the results will remain.

Reducing the time to market can make the implant more attractive for investors. Centralized market authorization through the European Medicines Agency (EMA) is compulsory for (c)ATMPs before national pricing and reimbursement decisions are made (291). Market authorization for cATMPs in the European Union (EU) has to pass through three committees: the Committee for Advanced Therapies (CAT: classifies, assess, and follows scientific progress of ATMPs regarding their safety, efficacy, and quality), the Committee for Medicinal Products for Human Use (CHMP: approves the scientific assessment of the application and recommend whether the ATMP should be marketed in the EU or not), and the Pharmacovigilance Risk Assessment Committee (PRAC). This process can take up to 277 days (292,293). Furthermore, in Europe cATMPs are regulated under the guidelines of medicinal products and medical devices (294), which may complicate the situation further. To facilitate the market authorization and the reimbursement process the EMA has made it possible for medicine developers to consult and work in parallel with EUnetHTA and HTA bodies. We support these possibilities because this may reduce the time to market and improve MS care (291). The early HTA presented in this thesis has not assessed the needs of the EMA and national HTA bodies, though including their voice early on may inform decision-making and help market authorization. Therefore, it would have been insightful to have consulted them along the way.

HEALTH TECHNOLOGY ASSESSMENT BODIES AND POLICYMAKERS

Untapped domains

Given the preclinical stage of the Optogenerapy implant, an in-depth analysis of all the HTA Core Model domains would perhaps have been too extensive. As such, this thesis dove into two of the nine HTA Core Model domains. One can wonder whether it is even feasible for early HTA to examine all nine domains, and perhaps that may only be achievable in later phases of the product development. However, an initial exploration of other domains, such as organizational aspects and an ethical analysis, are relevant for Optogenerapy but not examined in this thesis. Unfortunately, this is not an uncommon practice. HTA reports published by HTA agencies in the early 2000s primarily highlight the clinical effectiveness domain rather than organizational or patient aspects (295). A literature review by Nielsen et al. (2011) also noted that domains such as the organizational, ethical, and legal aspects are under-researched (296).

Assessing the organizational implementation of a new technology may occur at a macro-level (nationally) and micro-level (within an organization, for example at the hospital level) (33). Qualitative research methods such as interviews or focus groups with stakeholders (hospitals, patient advocacy groups, government bodies, industry logistics) should be held to investigate organizational aspects of the Optogenerapy implant. Issues such as cross-country logistics of transferring the genetically modified cells and assembling the device still have to be further explored. A start has been made regarding the health delivery process of the implant at the hospital level (see the treatment pathway presented in *Chapter 6*). However, we did not take into account aspects such as a learning curve for surgeons implanting the device or reorganizing the current workflow of the procedure room where the implantation takes place. While exploring the organizational implementation may be time-consuming and costly, the knowledge gained is crucial for the success of the implant. Therefore, it is reasonable to say that more emphasis on these aspects is needed in early HTA. Organizational aspects should not be overshadowed by domains such as safety and clinical effectiveness. Inevitably, if the device cannot reach the patient, then all the preclinical research will have been for nothing.

An early HTA of cATMPs should also try to provide answers to ethical concerns. Uncertainties about potential ethical implications and legal concerns regarding the lack of control of the genetically modified cells (the potential to develop malignancies if cells escape from the drug cell chamber), or consequences of gene therapy by changing the DNA of cells are elements that should be discussed in an HTA, though such ethical matters rarely are (297). In this thesis the ethical considerations were not examined. Knowing what ethical values are deemed important by society can help justify the development of novel medical technologies (297). Methods such as seeking advice from medical ethicists, conducting qualitative research and literature research on ethical issues are ways to analyze ethical aspects related to the Optogenerapy implant (297). Ethical analysis is complex which can make it a barrier in HTA. However, it should not be seen as less important than other domains of HTA such as the economic domain.

Inequal access to MS healthcare in Europe

Across Europe, the access to MS healthcare is inequal (2,44). Market authorization of new treatment is organized at a European level (by the EMA), however, the reimbursement decision is made at a national level (44). Regrettably, there are delays (of some years) between central EMA approval and national reimbursement of DMTs in EU countries (2). The diverse healthcare systems and HTA reimbursement decisions, sadly, do not encourage uniform access to healthcare (44). This is in stark contrast to every human being's *"right to the enjoyment of the highest attainable standard of physical and mental health"* (298). Reports have found that the reimbursements of DMTs are generally good, with 32 out of 35 EU countries involved in the European 2020 MS Barometer study offering at least one DMT with 100% reimbursement. However, this doesn't ensure equal access to DMTs: some countries require out-of-pocket payments, the organization of MS care may differ (some countries have dedicated MS centers while others have multi-disciplinary neurological units), and geographical challenges prohibiting accessibility of care. Consequently, treatment rates range from 6% to 90% across Europe (2).

Presently, it is unknown whether the Optogenerapy implant will reduce inequalities within the MS patient population or across countries. The implant has the potential to improve QOL and reduce administrative burden only for a select group of patients: persons with early RRMS, or currently taking injectable INFβ. However, this means that 10-15% of the MS patient population, those with either SPMS or PPMS, are not eligible. Therefore, it is also important to fund research to improve their QOLs and to try to reduce treatment inequalities within the MS population. Furthermore, one has to keep in mind that the external controller of the implant, the wireless powering belt needs recharging. Therefore, persons living in countries with poor electrical infrastructure are excluded from this novel device. HTA results are not easily transferable across countries (296,299), and implementing health interventions developed by wealthier nations may not hold in developing countries (300). This early HTA has not examined how the implant may be able to reduce inequalities in MS care, however reducing inequalities in healthcare is important to improve the overall health of persons with MS. It would be of interest to discuss these matters with governmental and health policy agencies, medical ethic experts, and health economists to address such matters on an (inter)national scale.

Challenges of clinical evidence generation

Reimbursement for (c)ATMPs may have challenges because clinical evidence generation may be difficult and perhaps a more lenient view towards the standards of clinical evidence generation is warranted. The EMA and HTA bodies might have to accept single-arm trials or observational level evidence regarding clinical effectiveness, rather than prefer results from RCT, even in the light of potential biases that may occur (301).

Some RCT-related challenges for Optogenerapy may be: ethical approval for a double-blinded RCT because of 'sham' surgery (301); the learning curve for the surgical team; and recruitment difficulties because patients may want to be treated with a more efficacious DMT.

Initially, surrogate outcome measures may be needed to validate therapeutic efficacy, for example by measuring biomarkers of INF secreted in the blood. Surrogate outcomes are not one-on-one identical to clinical outcome measures, but this highlights the need for long-term data (37).

Key players in the field of cell macroencapsulation technology (302) are further along in the development of drug-releasing devices. Examples can be found in disease areas such as Alzheimer's Disease (303), Parkinson's Disease (303), ocular diseases (304), and diabetes mellitus (305,306), which are at various clinical research stages. Their phase I/II safety, tolerability and efficacy studies are mainly non-randomized, single-arm trials with surrogate outcome measures (for example, adverse events, survival of tissue, cell loss) (305,306). One phase III trial is randomized but with a sham procedure as a comparator (304). The Optogenerapy consortium might look to them for lessons learnt.

The trial-related challenges may, down the line, also affect the price of the device. For now, we expect the acquisition costs of the implant to be €10.000, however, this is a ball-park estimate and future trials may turn out more costly than anticipated. The price of the device will for instance depend on the type of trial, duration, and the number of patients included. Nevertheless, the Optogenerapy implant was developed using high volume manufacturing techniques therefore mass fabrication is readily available to put the Optoferon devices into the market at a competitive cost.

The use of patient and ATMP registries can increase the body of (long-term) safety and efficacy data gathered. For Optogenerapy it will be important to monitor malignant transformations (cells escaping from the cell chamber) and observe how long the cells will maintain their therapeutic function and efficacy levels. Such long-term data is essential for market authorization and post-authorization follow-up studies (37,307).

Value assessment

The value of a medical device is traditionally explored by performing an (early) economic evaluation examining health effects expressed in quality-adjusted life years (QALYs) (133). However, this may not be the most relevant outcome measure for medical devices or cATMPs (37,297,308,309). The use of QALYs is practical because it creates a level playing field by enabling the ability to compare the health state of persons from different disease areas. As such, it is commonly used in economic evaluations. However, to base an economic evaluation and HTA recommendation on QALYs alone may be somewhat short-sighted. Therefore, the value assessment of should be explored from a broader perspective.

Including patient preferences in the HTA evaluation is a first step. If the new medical device or cATMP is aligned to the needs of the patient it creates more value for the patient. This preference value can be included in an economic evaluation. For example, in addition to the QALYs gained, examine the preferences gained (or the value of that preference gained).

Another step may be exploring the wellbeing of persons and include such a measure in the value assessment. Currently, research is being performed how to include such measures in the economic evaluation (310–312).

The Optogenerapy implant is a disruptive mode of treatment administration and this innovation may stimulate the development of other innovative drug delivery implants, leading to scientific spillover effects (37). Such spillover effects are important, creates value, and should be integrated into the economic evaluation more often. Notably, we should practice what we preach. This early HTA did not include such spillover effects, though the next steps of the implant development should look into this further. Using multi-criteria decision analysis (MCDA) methods and including all stakeholders involved can support decision making and determine the added value of spillover effects to society. This added value can be combined with cost data to determine the monetary value of each spillover effect which can then be included in the economic evaluation (313).

HEALTHCARE PROFESSIONALS

The results of this early HTA inform HCPs about the potential benefits and risks of this new mode of treatment administration. HCPs can envision the impact new medical technology will have in the clinic and determine whether it enhances the quality of care, i.e. is it effective, safe, and patient-centered (314)? However, the adoption of and intention to use HTA recommendations by HCPs depend on the attitudes towards the device (315). Technology will only be adopted if the cultural context has been properly prepared beforehand. This requires correct implementation and behavior change strategies (316). Underperformance (i.e. lower effectiveness) of health interventions in clinical practice may occur because of failing to address structural problems, cultural context-related factors, and lack of managerial or political support (316). Therefore, it is so important to have HCPs on board to examine the organizational structures of hospitals to prepare for the implementation of Optogenerapy in clinical practice.

The clinicians involved in the Optogenerapy consortium were partly responsible for organizing the next step of the project: the in-human clinical trial. To clinicians and HCP involved in developing the (randomized) clinical trials, we advise them to collect data on HRQOL during the clinical trials in addition to efficacy and safety data. Measuring HRQOL allows clinicians and other stakeholders involved to monitor and observe the current QOL status of their patients. Furthermore, we advise them to have focus group sessions with the patients to get a more hands-on feel of how the implant is affecting their lives and how the device has become a part of them. Finally, it is informative to continue collecting data post-trial to measure the quality of care, efficacy, or other patient-reported outcome measures by utilizing patient device registries (317).

PATIENT ORGANISATIONS

Patient preferences and views were explored in this early HTA. Including the voice of the patient in an early HTA is meaningful because they live with MS daily and have the best ability to determine how the device will affect their lives, and it increases the social legitimacy of healthcare decisions (318). However, neither a MS patient organization nor an MS foundation were partners of the Optogenerapy consortium. Patient organizations are a necessary partner in translational research because they can help disseminate project results to their members and the wider public, represent the view and preferences of patients within the partnership, and assist the development of the product (319). Health foundations can also be a valuable partner in public-private (research) partnerships because they too can provide access to patients, provide access to academic experts, attract additional funding, and emphasize the need for collaboration and information sharing (319). For future follow-up projects for Optogenerapy, a patient organization may fulfil an important role within the consortium.

LESSONS LEARNT AND FUTURE RECOMMENDATIONS

This early HTA examined and quantified the needs, preferences, and HRQOL of persons with MS. Furthermore, we explored the potential cost-effectiveness of the Optogenerapy cell-based drug delivery implant. Though the cost-effectiveness is the final analysis performed in this thesis, it is not the "final act" when assessing new medical technology and making recommendations. It is one of the ingredients needed to decide on whether medical technology developers should continue developing their products.

This thesis used a mixed-methods approach to determine the potential of the Optogenerapy device. And perhaps that it the most important lesson learnt, that performing qualitative and quantitative research gives a more holistic view of the potential of new medical

technology. Qualitative and quantitative research are not mutually exclusive, they are both needed to further the understanding of patient needs and tailor the device to their liking. But equally important are the needs and preferences of the other stakeholders involved to be able to align their needs such that the device has the greatest potential for success. An open dialogue between all the stakeholders is essential such that everybody is aware of the expectations and goals each stakeholder has.

This thesis dove into two of the nine domains presented by EUnetHTA, therefore leaving some domains somewhat untouched. The HTA Core Model is primarily aimed at a traditional HTA decision, though we find that it can be used to guide early HTA also. When used for an early HTA decision, exploratory research based on the domains is needed before the 'classical' HTA commences. Table 1 presents some recommendations through lessons learnt during the Optogenerapy project categorized per domain. To note, this does not mean that these recommendations should replace the work we performed, but should be seen in addition to the work. The recommendations indicate the type of research that can be conducted during device development, though are not limited to preclinical (early HTA) research. These recommendations are formulated for the Optogenerapy project, but may also be applicable for other translational research products focusing on medical device development.

In short, for medical device developers, it is advised to (at the very least) consult patient representatives during the device development. Also, explore the possibilities of secreting more efficacious second-line therapy by the genetically modified cells. Health technology bodies and policymakers are key players when it comes to organizational implementation of new medical devices. They have a responsibility to reduce accessibility inequalities of MS care across Europe by improving the supply chain of DMTs and aligning market authorization. Furthermore, using RCTs for clinical evidence generation may not hold for ATMPs, thus leniency in that regard is warranted. Finally, it is valuable to explore other measures in addition to the QALY to determine the value of ATMPs (such as stakeholder preferences and spillover effects). Healthcare professionals have to be included early on in device development and be involved with the early HTA to enhance successful implementation of the device in clinical practice. HCPs are in part responsible for the trial development and we advise them to include generic and disease-specific HRQOL measures along with organizing focus group sessions to examine the effects of the device. A group of people that should have been a stakeholder within the consortium are the persons with MS. They will be the end-users of the device and therefore have an important role in the development of the device, recruitment for trials, dissemination of results, and overall success of the Optogenerapy implant.

CONCLUSIONS

This thesis investigated the potential of the Optogenerapy cell-based drug delivery implant within the current treatment landscape in MS care. The early HTA analyses indicated that the implant indeed may potentially be an addition to the current treatment landscape and may replace current modes of treatment administration. For early HTA recommendations it is important to examine the value of a new medical technology using both quantitative and qualitative methods. All the relevant stakeholders should be included in the value assessment and be involved during the product development. For now, the Optogenerapy implant can be an alternative to injectable INFβ for persons with early RRMS eligible for INFβ therapy. Perhaps in the future the Optogenerapy implant may also be eligible for persons with more progressive MS. The overall goal is to improve the quality of care for all persons with MS, and the Optogenerapy implant may be one such device to do so.

Table 1 Future recommendations for medical technology developers

HTA Core Domain	Applicable for	What we did	Recommendations through lessons learnt
Patient and social aspects	Med tech developers	Focus group sessions and a stated preferences study (a DCE) towards the end of the Optogenerapy project (in year 3). In both cases we presented a mock-up of the device.	What: Focus group sessions / co-design sessions discussing and developing device design using prototypes (multiple sessions) Why: To adapt the device to the needs of the end-user When: Preclinical (translational research) With: Medical technology developers, patients, HCPs
	Med tech developers HCPs	See above	What: Focus group sessions / surveys Why: To determine whether the device does what it was intended to do When: Phase I-III trials (clinical research) With: Trial participants, HCPs involved in the trial
	Med tech developers HTA bodies/ policymakers	See above	What: Preference elicitation methods (MCDA) or qualitative methods (focus group sessions, Delphi method[a]) Why: To perform a value assessment of the implant When: Preclinical and clinical research With: Med tech developers, HCPs, patients, HTA bodies / policymakers, insurance company
	Med tech developers HTA bodies/ policymakers	Public-private partners within the Optogenerapy consortium	What: Include either a patient organization or a MS foundation as a consortium member Why: Persons with MS live with the disease and they will be the end-user of the device, to help disseminate project results When: Preclinical and clinical research With: (Representatives of) persons with MS
Health problem and current use technology	Med tech developers	Stated preference research (DCE, mean predicted uptake, trade-off research) including implant, pills, and injectable DMT	What: Stated preference research including infusion therapy Why: To examine the position of the device within the whole treatment landscape of MS When: Phase I-III (clinical research) With: Persons with MS
	Med tech developers	See above	What: SWOT/PEST analyses examining the position of Optogenerapy against 2nd-line DMT and aHSCT Why: Exploring market uncertainties When: Preclinical (translational research) With: HTA bodies/ policymakers, HCPs
	Med tech developers	Patient population: persons with RRMS eligible for INFβ treatment	What: Develop cell-lines that can secrete 2nd-line DMT Why: To treat all persons with MS (RRMS, PPMS, SPMS) When: Preclinical (translational research)

			With: Medical technology developers
Organizational aspects	HCPs	Assumption made regarding the possible Optogenerapy treatment pathway	What: Focus-group sessions / interviews to explore organizational aspects of implementing the technology in the hospital setting Why: HCP and managerial support needed for successful implementation of Optogenerapy in the healthcare setting When: Preclinical and clinical research With: HCPs, hospital managers
	HTA bodies/ policymakers	How to organize / implement Optogenerapy on an (inter)national scale was not examined	What: Focus group sessions / interviews to examine how the Optogenerapy can reduce inequal access to treatment across the EU Why: Inequal access to healthcare is unethical and against every human being right to health When: Phase I-III and before market access decisions are made With: HTA bodies / policymakers
	Med tech developers HTA bodies / policymakers	See above	What: Interviews to examine the Optogenerapy supply chain Why: Streamline the cross-country development process to reduce costs and know-how of relevant legislation When: Phase I-III and before market access decisions are made With: Med tech developers, supply-chain specialists, policymakers
Safety and clinical effectiveness	Med tech developers HTA bodies/ policymakers HCPs	Assumptions made on safety and efficacy profile of Optogenerapy based on literature search and expert opinion in the Netherlands	What: Multi-country (randomized) clinical trials (HTA bodies should have a lenient view towards the type of trials performed) Why: Efficacy and safety data is needed for the HTA and market authorization When: Phase I-III (clinical research) With: Patients, HCPs
	Med tech developers HTA bodies/ policymakers HCP Patients	See above	What: Collect long-term safety and efficacy data through patient device registries (follow-up study) Why: Market authorization, post-authorization, quality assurance When: Post-authorization (access and pricing) With: Patients, HCP involved in the trial and/or treating physicians
Cost effectiveness	HTA bodies/ policymakers	Markov model with assumptions	What: Piggy-back cost-effectiveness analysis Why: Reduce model and parameter uncertainties, better indication of the true cost-effectiveness of the device, market authorization When: Phase I-III (clinical research) With: HTA bodies/ policymakers

Ethical analysis and legal aspects	Med tech developers HTA bodies / policymakers HCP	An ethical analysis and legal aspects were not examined	What: Seeking advice from medical ethicists/legal experts on potential ethical issues of the Optogenerapy device Why: Have to be aware of potential ethical and legal consequences of the device When: Phase I-III (clinical research) With: Medical ethicists, legal, HCP, medical technology developers
Description and technical characteristics of technology	Med tech developers HTA bodies/ policymakers	A general overview of the Optogenerapy implant was provided	What: Full disclosure of the device needed for EMA approval Why: Needed for market authorization When: Clinical research and access and pricing With: Med tech developers

aHSCT: autologous hematopoietic stem cell transplantation, cATMP: combined advanced therapy medicinal product, DCE: discrete choice experiment, DMT: disease-modifying therapy, EMA: European Medicines Agency, EU: European Union, HCPs: healthcare professionals, HRQOL: health-related quality of life, HTA: health technology assessment, INFβ: beta-interferon, MCDA: multiple-criteria decision analysis, Med tech developers: medical technology developers, MS: multiple sclerosis, PEST: Political, Economic, Social, Technological, PPMS: primary progressive multiple sclerosis, RCT: randomized clinical trial, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis, SWOT: Strength, Weaknesses, Opportunities, and Threats,

[a] Delphi method: A research technique with a group of experts to obtain a reliable group opinion pertaining to a certain research question (320).

SUMMARY

Multiple sclerosis (MS) is a chronic neurological disease of the central nervous system (CNS) affecting young women and men. The course of MS is unpredictable and is characterized by neurological events of the CNS (called a relapse). Depending on the type of MS, persons may or may not fully recover from a relapse. Unfortunately, there is no cure for MS. Persons are treated with disease-modifying therapies (DMTs) to reduce disease progression and relapse rate. DMTs are taken via injection, orally, or intravenously, each with its own specific efficacy and safety profile. The Optogenerapy consortium aimed to develop and demonstrate a new mode of treatment administration for persons with MS: a wireless powered cell-based optogenetics implantable device to administer beta-interferon (INFβ). To examine the potential health economic impact of the Optogenerapy implant we performed an early health technology assessment (HTA). The overall aim of this thesis was to assess whether the Optogenerapy implant can be a potentially addition to the current treatment landscape in MS care.

To assess the potential of the implant we first examined the needs and preferences of relapsing-remitting multiple sclerosis (RRMS) patients during their treatment decision-making process by performing a systematic literature review *(Chapter 2)*. The treatment decision-making process was furthermore explored in two focus group sessions performed in the Netherlands *(Chapter 4)*. Patient preferences for treatment characteristics were investigated by performing a stated preference study (a discrete choice experiment; DCE) in three countries (the Netherlands, France, and the United Kingdom). The DCE examined the trade-offs persons with MS make regarding the mode of administration and treatment characteristics *(Chapter 5)*. Moreover, we examined the current health-related quality of life (HRQOL) status of persons with MS in Western Europe by performing a quality of life survey using generic and disease-specific measures *(Chapter 3)*. In that survey, we also explored the possible acceptance of implant therapy for MS. The focus group sessions, the DCE, and the HRQOL survey each examined the reasons given by the respondents for, and against, the implantable device as a new mode of administration. Finally, the knowledge gathered from all the conducted studies was utilized and used as input (parameters) for the cost-effectiveness analysis (CEA) *(Chapter 6)*.

Qualitative studies included in the systematic review found that patients initiate taking a DMT because they want to have some form of control over their disease. Persons with MS are encouraged to start a DMT as soon as possible. However, not much research has been conducted to determine what drives the patient to initiate their treatment course *(Chapter 2)*. By taking a DMT patients feel that they can control MS, either by having an influence over the disease progression or by having a say when and how the DMT is administered *(Chapter 2)*. We found that patients hold on to this throughout their disease course. The motivation for continuing or switching treatment is driven by the hope that the DMT will prevent a more severe disease state *(Chapter 4)*. Furthermore, MS and the treatment decision-making moments (to start, stop or switch DMT) are associated with uncertainty whilst having to deal with side effects, breakthrough disease (which may lead to a perceived lack of efficacy), and not knowing whether treatment affects the disease progression *(Chapter 4)*.

Quantitative studies included in the systematic review examined reasons for treatment non-adherence, discontinuation, or switching, along with patient preferences. We found that persons with MS are non-adherent or discontinue therapy because persons forget to administer the treatment, suffer from side effects, and a perceived lack of efficacy. Persons switch therapy because of poor tolerability, because the healthcare provider gives the advice to switch, or requested by the patient *(Chapter 2)*. The preference studies included in the systematic review found that RRMS patients prefer a DMT that decreases relapse rate and reduces the risk of (severe) side effects. Furthermore, oral treatment is preferred over injection or infusion therapy *(Chapter 2)*. We also noted that not many stated preference studies consulted with MS patients before developing the DCE to determine appropriate attributes and levels *(Chapter 2)*.

We examined patient preferences further by performing a DCE that quantified the preferences of persons with MS regarding three modes of administration (implant, pills, and injection therapy) and assessed the trade-offs patients are willing to make regarding treatment characteristics *(Chapter 5)*. Following good research practices, we performed focus group sessions to select DCE attributes. While no formal ranking technique was used during the focus group sessions, efficacy and safety were central themes *(Chapter 4)*. The DCE data was analyzed using a panel latent class multinomial logit model. We identified two preferences structures that mostly varied in whether the respondent would choose the treatments described to them or not (class 1 vs class 2, respectively). Preferences differed per type of MS, current DMT status, and mobility. In line with the results of the systematic review, we found that persons preferred a DMT that reduces relapse rate and disease progression. However, in contrast to previous studies, the safety profile (the side effects) was the least important attribute relative to the other attributes we examined. Furthermore, we found that patients were willing to accept an increase in the risk of relapse or disease progression to switch their treatment administration from injectable to the implant. Finally, we found that the mean predicted uptake was highest for the implant, followed by pills, injections, and no treatment *(Chapter 5)*.

Persons with MS have lower HRQOL than the general population and persons with other chronic diseases. Our HRQOL survey amongst real-world MS patients from several European countries confirmed this. The results highlight that the HRQOL reported in previously conducted clinical trials and observational studies may have been somewhat overestimated *(Chapter 3)*. Using both a generic QOL measure (the EuroQOL 5 dimensions with 5 levels; EQ-5D-5L) and a hybrid disease-specific QOL measure (the Multiple Sclerosis Quality of Life; MSQOL-54 including the generic SF-36) in a real-world setting can further the understanding of the HRQOL status of MS patients and shine a light on areas of care that need improving.

To develop the conceptual model for the economic evaluation of the Optogenerapy implant and estimate the health outcomes and costs it was necessary to gain insight into the preferences, needs, and HRQOL of patients. Furthermore, those insights enabled us to draw conclusions beyond cost-effectiveness. The potential cost-effectiveness of the Optogenerapy implant was investigated in the Dutch healthcare setting. The baseline characteristics of the patients included in the model were based on the data collected from the HRQOL survey *(Chapter 3)*. The molecular composition of the INFβ-1a secreted by the genetically modified cells is most similar to the composition of INFβ-1a of the DMT Avonex. Therefore, we used Avonex as the comparator in the analysis. Moreover, the efficacy and safety profile of Avonex was used to populate the model. Results from the systematic review showed that the percentage of patients not missing a single injection ranged from 63-75% *(Chapter 2)*. Therefore, we modelled 100% adherence for patients having the implant. We took the non-adherence of injectable therapy into account by assuming a difference in annual relapse rate between the implant and injectable therapy (in favor of the implant). Furthermore, we assumed that persons receiving the implant would be less likely to withdraw from treatment.

We found that the implant, compared to injectable INFβ, has the potential to be very cost-effective. The Optogenerapy implant has the potential to reduce healthcare costs (-€34,099) and improve health outcomes (0.49 quality-adjusted life years; QALYs gained). However, as long as the implant fulfils expectations regarding safety, efficacy, and acquisition costs *(Chapter 6)*. The lower acquisition costs and the lower withdrawal rates for the implant were the main drivers of cost-effectiveness. The only parameter that may harm the cost-effectiveness of the implant (i.e. more in favor of injectable therapy) was when the rate of disability progression of Avonex was improved (greater treatment efficacy for Avonex). Our findings suggest that implant therapy remains a dominant strategy in three scenarios: doubling the acquisition costs to €20,000, hospitalizing the patients one night for implantation (and removal), and setting the withdrawal rates equal. Also, the Optogenerapy implant would remain cost-effective if the implant were to be implanted and replaced yearly *(Chapter 6)*. The DCE results found that persons with MS have similar utility

preferences for replacing the implant yearly or once per three years *(Chapter 4)*. This can be helpful when making final decisions regarding a yearly or three-yearly replacement. To ensure that the implant is still cost-effective compared to Avonex, at a willingness to pay (WTP) threshold of €50,000/QALY, the headroom (i.e. the maximum additional costs of the implant over Avonex) was calculated at €58,557.

We aimed to assess whether the Optogenerapy cell-based drug delivery implant can potentially be an addition to the current treatment landscape in MS care. The findings from this thesis indicate that the implant indeed may potentially be an addition to the current treatment landscape. However, some lessons learned have to be taken into consideration before the next steps regarding product development are made.

For medical device developers, it is advised to include patient representatives during the device development and to explore the development of secreting more efficacious second-line therapy by the cells in the device. The reasons are three-fold: firstly, including the patients' voice is essential for device development to align the needs of the patient to that of the device, secondly, limiting oneself to INFβ reduces the potential of the device because you target a select patient population (persons with early RRMS), thirdly, while INFβ is still one of the most prescribed DMTs, it is not the most efficacious DMT and persons prefer their treatment to reduce disease progression and relapse rate. It would be ideal if the cells inserted into the device could be removed easily, so for example start with a first-line therapy, and if deemed necessary remove and replace the cells with second-line therapy.

Health technology bodies and policymakers have an important role in reducing healthcare inequalities for persons with MS regarding the accessibility of DMTs in Europe. Therefore they have a role in examining how the Optogenerapy device can help reduce these inequalities. Furthermore, the organizational implementation of a medical device at a national and EU level should not be overlooked in an early HTA. If the device cannot reach the patient, then the time and costs on preclinical research will have been wasted. Furthermore, the preferred clinical evidence generation for cost-effectiveness (RCTs) may not hold for ATMPs and perhaps a more lenient approach is warranted. Additionally, more patient-centric disease-specific measures, and examining spill-over effects are perhaps more in place when determining the value of an ATMP and its cost-effectiveness rather than focusing on the QALYs alone.

Health care professionals (HCP) are responsible for prescribing treatment to persons with MS and their prescribing habits can impact the success of the device. If HCPs do not see the added benefit of the implant, they will not prescribe it to their patients, rendering this novel translational research useless. Together with patient representatives they are important stakeholders to be involved in device development and during the early HTA. Also, the HCPs are responsible for the trial development, and we advise them to include generic and disease-specific quality of life measures along with other patient-relevant outcome measures.

For patients, their input in device development is very important. They will be the end-user of the implant, and if they do not feel that the device will improve their quality of life they will not choose the implant when presented to them as a treatment option. The role of patient representatives in product development and the early HTA may still be undervalued, while this thesis has showed that their insight are most definitely of value. Therefore, future research consortiums should have a patient representative as stakeholder.

NEDERLANDSE SAMENVATTING

Multiple sclerose (MS) is een chronische neurologische aandoening van het centrale zenuwstelsel die jonge vrouwen en mannen treft. Het beloop van MS is onvoorspelbaar en wordt gekenmerkt door neurologische aanvallen van het centrale zenuwstelsel (een 'relapse' genoemd). Afhankelijk van het type MS kunnen personen al dan niet volledig herstellen van een relapse. Helaas is er geen genezing mogelijk voor personen met MS. Personen worden daarom behandeld met ziekte modificerende therapieën (disease-modifying therapies: DMT's) om de ziekteprogressie en terugval te verminderen. DMT's worden via een injectie, oraal of intraveneus toegediend, elk met hun eigen specifieke werkzaamheids- en veiligheidsprofiel. Het doel van het Optogenerapy consortium was een nieuwe toedieningsvorm voor de behandeling van MS te ontwikkelen en te demonstreren: een draadloos aangedreven, cell-based implanteerbaar optogenetics device, om interferon bèta (INFβ) toe te dienen. Om de potentiële gezondheidseconomische impact van het Optogenerapy-implantaat te onderzoeken, hebben we een vroege health technology assessment (HTA) uitgevoerd. Het doel van dit proefschrift was om te beoordelen of het Optogenerapy implantaat een mogelijke aanvulling kan zijn binnen de huidige behandelopties voor personen met MS.

Om de potentiële impact van het implantaat te beoordelen, onderzochten we eerst de behoeften en voorkeuren van patiënten met relapsing-remitting multiple sclerose (RRMS) tijdens hun behandel-gerelateerde besluitvormingsproces. Dit is onderzocht door middel van een systematische literatuurstudie *(Hoofdstuk 2)*. Het besluitvormingsproces over de behandeling werd verder onderzocht in twee focusgroep sessies die in Nederland zijn gehouden *(Hoofdstuk 4)*. Patiëntvoorkeuren voor behandelkenmerken werden onderzocht door het uitvoeren van een patiënt preferentiestudie (een discrete choice experiment; DCE) in drie landen (Nederland, Frankrijk en het Verenigd Koninkrijk). De DCE onderzocht de afwegingen die personen met MS maken met betrekking tot de wijze van toediening en behandelingskenmerken *(Hoofdstuk 5)*. Ook hebben we de huidige gezondheidsgerelateerde kwaliteit van leven (HRQOL) status van personen met MS in West-Europa onderzocht door het uitvoeren van een kwaliteit van leven onderzoek met behulp van generieke en ziektespecifieke vragenlijsten *(Hoofdstuk 3)*. In dat onderzoek hebben we ook de mogelijke acceptatie van het toedienen van behandeling door middel van een implantaat onderzocht. De focusgroep sessies, de DCE en de HRQOL-studie onderzochten ieder waarom respondenten voor of tegen het gebruik zouden zijn van een implantaat als nieuwe toedieningsvorm. Ten slotte is de kennis uit alle onderzoeken verzameld en gebruikt als bouwstenen voor de kosteneffectiviteitsanalyse (KEA) *(Hoofdstuk 6)*.

Kwalitatieve studies die in de systematische review zijn opgenomen, hebben aangetoond dat patiënten beginnen met het gebruik van een DMT omdat ze graag controle over hun ziekte willen hebben. Mensen met MS worden aangemoedigd om zo snel mogelijk met een DMT te beginnen. Er is echter niet veel onderzoek gedaan om te bepalen wat de patiënt ertoe aanzet om met de behandeling te beginnen *(Hoofdstuk 2)*. Door een DMT te nemen, hebben patiënten het gevoel dat ze MS kunnen beheersen, hetzij door invloed te hebben op het ziekteprogressie, hetzij door zeggenschap te hebben wanneer en hoe de DMT wordt toegediend *(Hoofdstuk 2)*. We ontdekten dat patiënten dit gedurende hun ziekteverloop vasthouden. De motivatie om de behandeling voort te zetten of te veranderen wordt gedreven door de hoop dat de DMT een ernstiger ziektetoestand zal voorkomen *(Hoofdstuk 4)*. MS en de behandelbesluiten (starten, stoppen of veranderen van DMT) zijn geassocieerd met onzekerheid terwijl men ook te maken heeft met bijwerkingen, doorbraak van ziekte (wat kan leiden tot een waargenomen gebrek aan werkzaamheid) en niet weten of de behandeling de ziekteprogressie beïnvloedt *(Hoofdstuk 4)*.

Kwantitatieve studies die in de systematische review zijn opgenomen, onderzochten de redenen voor het niet naleven, stopzetten of veranderen van de behandeling, samen met de voorkeuren van de patiënt. Personen met MS zijn therapieontrouw of staken de therapie omdat zij vergeten de behandeling toe te dienen, last hebben van bijwerkingen en een vermeend gebrek aan

werkzaamheid. Mensen wisselen van therapie vanwege een slechte verdraagbaarheid, omdat de zorgverlener het advies geeft om over te stappen, of op verzoek van de patiënt *(Hoofdstuk 2)*. Uit de preferentiestudies die in de systematische review zijn opgenomen, bleek dat RRMS-patiënten de voorkeur geven aan een DMT die het terugvalpercentage verlaagt en het risico op (ernstige) bijwerkingen verkleint. Bovendien heeft orale behandeling de voorkeur boven injectie- of infusietherapie *(Hoofdstuk 2)*. We zagen ook dat weinig onderzoeken voorafgaand aan het ontwikkelen van een DCE met patiënten overlegden om de juiste attributen en levels te bepalen *(Hoofdstuk 2)*.

We onderzochten de voorkeuren van de patiënt door een DCE uit te voeren waarin de voorkeuren van mensen met MS werden gekwantificeerd met betrekking tot drie toedieningswijzen (implantaat, pillen en injectietherapie). Ook onderzochten we de afwegingen die patiënten bereid zijn te maken met betrekking tot behandelingskenmerken *(Hoofdstuk 5)*. Op naleving van de onderzoek richtlijnen hebben we focusgroep sessies gehouden om DCE attributen te selecteren. Hoewel er geen formele rangschikkingstechniek werd gebruikt tijdens de focusgroep sessies, waren werkzaamheid en veiligheid centrale thema's *(Hoofdstuk 4)*. De DCE werden geanalyseerd met behulp van een panel latent class multinomial logit model. We identificeerden twee voorkeurenstructuren die voornamelijk varieerden in de vraag of de respondent de beschreven behandelingen zou kiezen of niet (respectievelijk klasse 1 versus klasse 2). Voorkeuren verschilden per type MS, huidige DMT-status en mobiliteit. In lijn met de resultaten van de systematische review, vonden we dat personen de voorkeur gaven aan een DMT die het terugvalpercentage en ziekteprogressie vermindert. In tegenstelling tot eerdere onderzoeken was het veiligheidsprofiel (de bijwerkingen) echter het minst belangrijke kenmerk ten opzichte van de andere kenmerken die we onderzochten. Bovendien ontdekten we dat patiënten bereid waren om een toename te accepteren op de kans van terugval of ziekteprogressie door over te stappen van injecties naar implantaat. Ten slotte ontdekten we dat de gemiddelde acceptatie het hoogst was voor het implantaat, gevolgd door pillen, injecties en geen behandeling *(Hoofdstuk 5)*.

Personen met MS hebben een lagere kwaliteit van leven dan de algemene bevolking en personen met andere chronische ziekten. Onze HRQOL studie met real-world MS-patiënten uit verschillende Europese landen bevestigde dit. De resultaten benadrukken dat de HRQOL die in eerder uitgevoerde klinische onderzoeken en observationele studies werd gerapporteerd, enigszins overschat waren *(Hoofdstuk 3)*. Gebruikmakend van zowel een generieke kwaliteit van leven vragenlijst (de EuroQOL 5-dimensies met 5 niveaus; EQ-5D-5L) als een hybride ziektespecifieke kwaliteit van leven vragenlijst (de Multiple Sclerosis Quality of Life; MSQOL-54 inclusief de generieke SF-36) onder real-world patiënten het begrip van de HRQOL-status van MS-patiënten bevorderen en een licht werpen op zorggebieden die verbeterd moeten worden.

Om het conceptuele model voor de economische evaluatie van het Optogenerapy implantaat te ontwikkelen en de gezondheidsresultaten en kosten in te schatten, was het nodig om inzicht te krijgen in de voorkeuren, behoeften en HRQOL van patiënten. Bovendien hebben deze inzichten ons in staat gebracht om conclusies te trekken die verder gaan dan kosteneffectiviteit. De potentiële kosteneffectiviteit van het Optogenerapy implantaat werd onderzocht in de Nederlandse gezondheidszorg. De basiskenmerken van de patiënten die in het model zijn opgenomen zijn gebaseerd op de gegevens die werden verzameld uit de HRQOL studie *(Hoofdstuk 3)*. De moleculaire samenstelling van de INFβ-1a die door de genetisch gemodificeerde cellen van de implantaat wordt uitgescheiden, lijkt het meest op de samenstelling van INFβ-1a van de DMT Avonex. Daarom hebben we Avonex als comparator in de analyse gebruikt. Het werkzaamheids- en veiligheidsprofiel van Avonex werd gebruikt als input voor het model. Resultaten van de systematische review lieten zien dat het percentage patiënten dat geen enkele injectie overslaat varieert tussen de 63-75% *(Hoofdstuk 2)*. Vandaar dat wij hebben aangenomen dat personen met een implantaat 100% therapietrouw zijn, en zo meegenomen in het model. Therapie ontrouwbaarheid van injectie therapie is meegenomen in het model door een verschil aan te nemen in het jaarlijkse terugvalpercentage tussen het implantaat en de injectie therapie (in het voordeel

van het implantaat). Verder zijn wij er vanuit gegaan dat personen die het implantaat kregen minder snel zouden stoppen met de behandeling.

Het implantaat, in vergelijking met injecteerbare INFβ, heeft de potentie om zeer kosteneffectief te zijn. Het Optogenerapy implantaat kan de zorgkosten verlagen (- € 34.099) en de gezondheidsresultaten verbeteren (0,49 voor kwaliteit gecorrigeerde levensjaren; gewonnen QALY's). Echter, zolang het implantaat voldoet aan de verwachtingen met betrekking tot veiligheid, werkzaamheid en acquisitiekosten *(Hoofdstuk 6)*. De lagere acquisitiekosten en de lagere percentage van personen die stoppen met de behandeling van het implantaat waren de belangrijkste factoren voor kosteneffectiviteit. De enige parameter die een ongunstig effect heeft op de kosteneffectiviteit van het implantaat (d.w.z. meer ten gunste van injectie therapie) was wanneer de effectiviteit van Avonex werd verbeterd. Onze bevindingen suggereren dat het implantaat een dominante strategie blijft in drie scenario's: bij verdubbeling van de acquisitiekosten tot € 20.000, bij opname in het ziekenhuis voor de implantatie (en verwijderen) van het implantaat, en wanneer een gelijk aantal patiënten stoppen met de behandeling. Ook blijft het Optogenerapy implantaat kosteneffectief als het implantaat jaarlijks wordt geïmplanteerd en vervangen *(Hoofdstuk 6)*. Uit de DCE studie bleek dat personen met MS vergelijkbare voorkeuren hebben wat betreft het vervangen van de implantaat (jaarlijks of eens per drie jaar) *(Hoofdstuk 4)*. Dit kan handig zijn bij het nemen van definitieve beslissingen over een jaarlijkse of driejaarlijkse vervanging. Om ervoor te zorgen dat het implantaat nog steeds kosteneffectief is in vergelijking met Avonex, bij een bereidheid om te betalen (WTP) -drempel van € 50.000 / QALY, werd de headroom (d.w.z. de maximale extra kosten van het implantaat ten opzichte van Avonex) berekend op € 58.557.

We wilden beoordelen of het Optogenerapy implantaat als toedieningsvorm een aanvulling kan zijn binnen de huidige zorg voor MS. De bevindingen van dit proefschrift geven aan dat het implantaat inderdaad mogelijk een aanvulling kan binnen de huidige zorg voor MS. Er moet echter rekening worden gehouden met enkele resultaten voordat de volgende stappen met betrekking tot productontwikkeling worden gezet.

Voor ontwikkelaars van medical devices is het raadzaam om patiënt vertegenwoordigers mee te nemen tijdens de ontwikkeling van het device. Verder is het raadzaam om te onderzoeken of het mogelijk is om effectievere tweedelijnstherapie te produceren in de implantaat. Redenen hiervoor: ten eerste is het opnemen van de stem van de patiënt essentieel voor de ontwikkeling van het device en om de behoeften van de patiënt af te stemmen op de device, ten tweede wordt de potentie van het implantaat niet volledig benut als de ontwikkeling beperkt blijft tot INFβ (richt zich op een selecte groep patiënten - alleen personen met vroege RRMS), ten derde, INFβ mag dan wel nog steeds een van de meest voorgeschreven DMTs zijn, het is niet de meest effectieve behandeling en personen met MS geven de voorkeur aan een behandeling met hoge effectiviteit. Het zou ideaal zijn als de cellen die in het apparaat zijn ingebracht gemakkelijk kunnen worden verwijderd, dus bijvoorbeeld beginnen met een eerstelijnsbehandeling en indien nodig de cellen verwijderen en vervangen door tweedelijnstherapie.

Op het internationale niveau spelen gezondheidszorg beleidsmakers een belangrijke rol bij het verminderen van de ongelijkheden in de gezondheidszorg voor personen met MS met betrekking tot de toegankelijkheid van DMT's in Europa. Beleidsmakers hebben een rol bij het onderzoeken hoe het Optogenerapy implantaat deze ongelijkheden kan helpen verminderen. De organisatorisch-gerelateerde aspecten bij de implementatie van een medical device op nationaal en EU-niveau mag niet over het hoofd worden gezien in de beoordeling van een vroege HTA. Het is een verspilling van tijd en van preklinisch gerelateerde kosten als het device de patiënt niet kan bereiken. Het is mogelijk dat het genereren van klinisch bewijs voor economische evaluaties door middel van randomized controlled trials (RCTs) niet mogelijk is voor ATMPs, en dat een mildere benadering gerechtvaardigd is. Het gebruik van patiëntgerichte ziektespecifieke meetinstrumenten, en het onderzoeken en meenemen van spillover effects zijn wellicht meer van toepassing bij het

bepalen van de waarde, en de kosteneffectiviteit, van een ATMP dan wanneer men alleen op de QALYs focust.

Zorg professionals zijn verantwoordelijk voor het voorschrijven van een behandeling aan personen met MS en hun voorschrijfgewoonten kunnen het succes van het implantaat beïnvloeden. Als zorg professionals het voordeel van het implantaat niet zien, zullen zij het hun patiënten niet voorschrijven, waardoor het zin het van onderzoek naar deze nieuwe toedieningsvorm ongedaan wordt. Samen met vertegenwoordigers van patiënten zijn zorg professionals belangrijke stakeholders die betrokken moeten worden bij de ontwikkeling van medical devices en gedurende de vroege HTA. De zorg professionals zijn ook verantwoordelijk voor de verdere ontwikkeling van het onderzoekstraject en we raden hen aan om generieke en ziektespecifieke kwaliteit van leven vragenlijsten op te nemen, samen met andere patiëntrelevante uitkomstmaten.

De inbreng van patiënten bij de ontwikkeling van medical devices erg belangrijk. Zij zullen de eindgebruiker van het implantaat zijn, en als ze niet het gevoel hebben dat het apparaat hun kwaliteit van leven zal verbeteren, zullen ze niet voor het implantaat kiezen als het aan hen wordt aangeboden als toedieningsvorm. De rol van patiëntvertegenwoordigers in productontwikkeling en de vroege HTA wordt nog steeds ondergewaardeerd, terwijl dit proefschrift laat zien dat hun inzicht zeker waardevol is. Daarom zouden toekomstige onderzoeksgroepen een patiëntvertegenwoordiger als belanghebbende moeten hebben.

PHD PORTFOLIO

	Year	ECTS
Courses		
Qualitative interview techniques	2017	2
Systematic literature retrieval in PubMed, part I	2018	0,1
Systematic literature retrieval in PubMed, part II	2018	0,1
Qualitative data analysis with grounded theory	2018	2,5
Qualitative coding with ATLAS.ti	2018	1,5
Advanced decision analytic modelling methods for economic evaluations	2018	2
Choice modelling and stated choice survey design	2018	2
Project Management in Practice	2019	2,5
Basic didactics & course dynamics	2019	1
The power of LinkedIN	2020	1
Finance for non-financial managers	2020	2
Teaching activities		
Bachelor thesis supervision (2 students)	2017	2
Statistiek (M&T2)	2018	0,5
Kwaliteit van Zorg (Bachelor year 1)	2018	0,5
Bachelor thesis supervision (2 students)	2018	2
NIHES Health Economics Summer Course	2018	0,2
Hoe houden we de zorg betaalbaar?	2018	0,3
Kwaliteit van Zorg (Bachelor year 1)	2019	0,5
Bachelor thesis supervision (1 student)	2019	1
Master thesis supervision (3 students)	2019	4,5
NIHES Health Economics Summer Course	2019	0,2
Statistiek A	2019	0,5
Lecture "Health sector costs" (Master EuHEM)	2019	0,8
Hoe houden we de zorg betaalbaar?	2020	0,3
Conferences		
MSMS Conference Nieuwegein	2017	1
lolaHESG	2018	1
ISPOR Europe 2018 (poster presentation)	2018	1
ZorgSamenEvent	2019	1
IAHPR 10th Meeting	2019	1
lolaHESG (paper discussion)	2020	1
MultiJuseII (paper discussion)	2020	1
Other		
Member of the ESHPM Activities committee	2018-2020	2
Board member youngESHPM	2020-2021	1
Total		*40*

LIST OF PUBLICATIONS

INCLUDED IN THIS DISSERTATION

Patient needs and preferences in relapsing-remitting multiple sclerosis patients: A systematic review
L.A. Visser, C. Louapre, C.A. Uyl-de Groot, W.K. Redekop. Multiple Sclerosis and Related Disorders. (2020) 39:101929

Health-related quality of life of multiple sclerosis patients: a European multi-country study
L.A. Visser, C. Louapre, C.A. Uyl-de Groot, W.K. Redekop. Archives of Public Health. (2021) 79:39

Innovative medical technology and the treatment decision-making process in multiple sclerosis: A focus group study to examine patient perspectives
L.A. Visser, M. de Mul, W.K. Redekop. Patient Preference and Adherence. (2021) 15: 927-937

An implantable device to treat Multiple Sclerosis: A discrete choice experiment on patient preferences in three European countries
L.A. Visser, S.P.I. Huls, C.A. Uyl-de Groot, W.K. Redekop. Journal of Neurological Sciences (2021)

The potential cost-effectiveness of a cell-based bioelectronic implantable device delivering interferon beta 1a therapy versus injectable interferon beta 1a treatment in relapsing-remitting multiple sclerosis
L.A. Visser, M. Folcher, C. Delgado Simao, B. Guiterrez Arechederra, E. Escudero, C.A. Uyl-de Groot, W.K. Redekop. PharmacoEconomics (2021)

NOT INCLUDED IN THIS DISSERTATION

The Methodological Quality and Challenges in Conducting Economic Evaluations of Newborn Screening: A Scoping Review.
P. Cacciatore, L.A. Visser, N. Buyukkaramikli, van der Ploeg, C.P.B., van den Akker-van Marle, M.E. International Journal of Neonatal Screening (2020) 6, 94.

The potential cost-effectiveness of a machine learning tool that can prevent untimely ICU-discharge.
J. de Vos, L.A. Visser, A. de Beer, P. Thoral, P. Elbers, M. Fornasa, G. Cinà. Value in health (2021)

A tailored cardiac rehabilitation program for patients with obesity: a cost-effectiveness analysis.
L.A. Visser, I. den Uijl, W.K. Redekop, M. Sunamura, M. Lenzen, H.J. Stam, E. Boersma, R.W.M. Brouwers, H.M.C. Kemps, H.J.G. van den Berg-Emons, N. ter Hoeve. Working paper.

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
BSC	Best supportive care
BWS	Best-worst scaling
CA	Conjoint analysis
cATMP	Combined advanced therapy medicinal product
CBA	Cost-benefit analysis
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standard
CMA	Cost-minimization analysis
CNS	Central nervous system
CUA	Cost-utility analysis
DCE	Discrete choice experiment
DMF	Dimethyl fumarate
DMT	Disease-modifying therapy
DSA	Deterministic sensitivity analysis
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EQ-5D-5L	EuroQOL 5 Dimensions with 5 levels
EQ-VAS	EuroQOL Visual analogue scale
EUnetHTA	European network for Health Technology Assessment
FDA	Food and Drug Administration
GA	Glatiramer acetate
GP	General practitioner
HR	Hazard ratio
HRQOL	Health-related quality of life
HTA	Health Technology Assessment
i.m.	Intramuscular
ICER	Incremental cost-effectiveness ratio
INFβ	Beta-interferon
LY	Life year
MAR	Maximum acceptable risk
MCDA	Multiple criteria decision analysis
MHCS	Mental health composite score
MRI	Magnetic resonance imaging
MNL	Multinomial logit model
MS	Multiple sclerosis
MSQOL-54	Multiple Sclerosis Quality of Life 54
NHS	National Health Service
NIR	Near-infrared
NTZ	Natalizumab
PHCS	Physical health composite score
PICO	Patient Intervention Comparator Outcome
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary progressive multiple sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROMs	Patient-reported outcome measures
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QOL	Quality of life
R&D	Research and development
RCT	Randomized clinical trials
RRMS	Relapsing-remitting multiple sclerosis
s.c.	Subcutaneous
SE	Standard error
SF-36	Medical Outcomes Short Form 36
SF-36 MCS	SF-36 Mental composite score
SF-36 PCS	SF-36 Physical composite score

SPMS	Secondary progressive multiple sclerosis
SSI	Surgical site infection
UK	United Kingdom
USA	United States of America
WTP	Willingness to pay

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Ik weet bijna zo goed als de dag van gister hoe de tweede lezer van mijn master thesis van Health Economics, Policy and Law aan mij vroeg: wat wil je na je master gaan doen? Mijn antwoord daarop: mijn geneeskunde combineren met health economics. Nog geen paar weken later kreeg ik van die tweede lezer een uitnodiging om te solliciteren voor een PhD positie. En wie was die tweede lezer? Ken Redekop, mijn co-promotor. Dus ik kan niemand anders dan Ken als eerste bedanken. Bedankt om mij aan te nemen, om mij te steunen (want laten we eerlijk zijn, leuk vond ik het doen van de PhD niet altijd), om mij te helpen met mijn eindeloze vragen over cost-effectiveness models en bedankt dat je het keer op keer hebt willen uitleggen. Wat ben ik blij dat jij mijn co-promoter bent.

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ABOUT THE AUTHOR

Laurenske Aleida Visser was born on September 16, 1988 in Guildford, the United Kingdom. Growing up in the UK, Nigeria, and China she moved with her family to Noordwijk in the Netherlands, in 2004. After graduating high school in 2006 she moved to Amsterdam to study Medicine at the Vrije Universiteit. Her life-long dream to become a doctor became reality in 2016. Throughout her medical studies she realized that while she is passionate about healthcare, her contribution to the healthcare sector would go via another route rather than by standing at the bedside of patients as a doctor. As such, she received her second master's degree in Health Economics, Policy and Law at the Erasmus University Rotterdam in 2017. She was given the opportunity to work as a PhD candidate at the Erasmus School of Health Policy & Management faculty that same year. From 2017 to 2021 her research focused on the early health technology assessment of a new medical device for persons with multiple sclerosis as a member of the Optogenerapy consortium, a European Horizon 2020 project. During her PhD trajectory she missed the connection to the medical world, therefore she worked as a medical doctor at the Hyperbaar Geneeskundig Centrum te Rijswijk one evening per week from 2019 to 2021. In April 2021 she started as a Clinical Scientist at Philips Research exited to continue working with medical devices and still driven to make healthcare better for patients and physicians.

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