Societal Cost of **Multiple Sclerosis** in Ireland 2015

MSIreland
THE MULTIPLE SCLEROSIS SOCIETY OF IRELAND

UCD DUBLIN

Supported by
NOVARTIS

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MS Ireland would like to acknowledge the contribution of Aidan Larkin (National Services Development Manager; MS Ireland), Killian O'Rourke (Consultant Neurologist at MMUH & Clinical Lecturer at UCD), Chris McGuigan (Consultant Neurologist at SVUH and Clinical Lecturer at UCD), Derek O'Boyle (PhD student at NUI Galway), and Peter Carney (Health Economist, Novartis Ireland). The work of Shauna Preston (graduate intern at Novartis Ireland) is also acknowledged.

We thank all the people with MS who took the time to respond to our survey and Novartis Ireland for funding this important research.

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Societal Cost of Multiple Sclerosis 2015

9,000
people with MS

92% experience fatigue due to MS

41% say they relapsed in the last year

33% diagnosed with depression

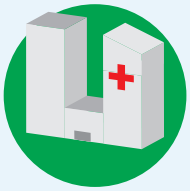
People with MS require a lot of care

- 54,000 GP visits/year
- 16,450 nights in hospital
- 1,544 emergency department visits (not admitted)
- 7,600 visits from MS Ireland caseworkers

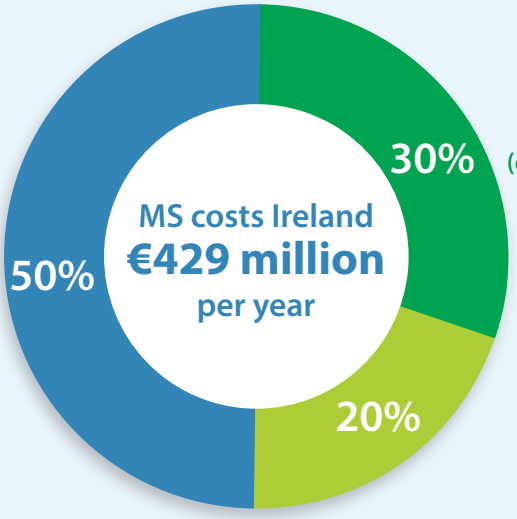
21,800
Neurology visits per year

MS is associated with HIGH costs.

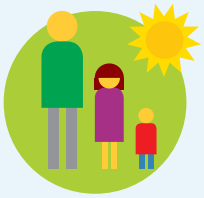
Most of these are *OUTSIDE* the healthcare system.



Direct cost
(e.g. hospitals, doctors, medication)

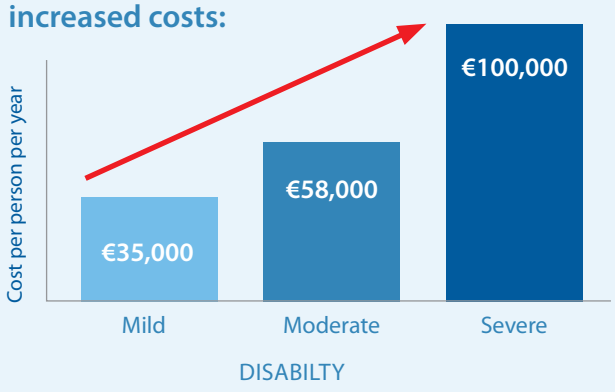


Indirect costs
(e.g. time off work, carers)



Intangible costs
(e.g. quality of life)

Disability progression associated with increased costs:



Cost of relapses in Ireland:
€16.9 million

Estimated savings from relapses avoided:
up to €10 million

Estimated savings from delayed disability:
up to €19 million

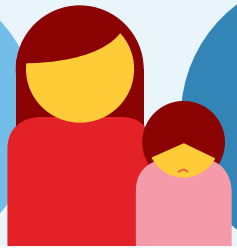
MS: A chronic disabling disease affecting people in their prime of life

Treatment & disease management can improve the ability of people to remain employed

- 7 out of 10 employees say MS has limited their career potential
- 34% of employees had to **REDUCE** working hours
- 900,000 days lost due to stopping work, absenteeism and presenteeism

MS is a disease of **ADULTS** but ***CHILDREN*** are affected

61% feel they can't financially provide for their children



73% of children worry about parents' health

Quality of Life is rated 32% less than for the general population and is lower in men than women

Recommendations

1. Access to interventions that reduce relapses and disability progression, support working and living independently
2. Improving employment opportunities

References
1. Societal Cost of Multiple Sclerosis in Ireland 2015

Date of preparation: October 2015

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2. Introduction

Multiple sclerosis (MS) is a complex, chronic inflammatory disease of the central nervous system (CNS). The condition is characterised by demyelination and axonal loss, resulting in neurological functional impairment and for many, ultimately leading to high levels of disability. Although the course of MS varies, 50% of people with the condition will need assistance with walking within 15 years after the onset of disease (Cottrell et al., 1999). In young adults, MS is the most common chronic disabling disease of the CNS, with the onset of the disease typically arising between 20 to 40 years of age (McDonald and Compston, 2006). As well as functional impairment and disability, common symptoms of MS include visual disturbances, altered sensation and abnormal speech, swallowing disorders, fatigue, bladder and bowel problems, sexual dysfunction and mood impairment (Trisolini et al., 2010). Relapsing-remitting MS (RRMS) is the most common form of MS, with approximately 80-85% of all people with MS experiencing a relapsing–remitting (RR) onset of the disease, with around 65% of those, in time, entering the secondary progressive phase (SPMS) (Balk et al., 2014). RRMS is characterised by episodic exacerbations of neurological signs or symptoms which typically appear over a period of several days and stabilise, with complete or partial recovery. As the signs and symptoms of CNS dysfunction persist after relapses, or progression occurs between relapses, the diagnosis progresses to SPMS. A smaller proportion of people present with primary progressive MS (PPMS), for whom progressive neurological disability occurs from onset (Patwardhan et al., 2005).

It is estimated that the total number of people living with MS worldwide is 2–2.5 million, with prevalence estimates varying from <5 cases per 100,000 people in Asia to 100-200 per 100,000 people in the US and Northern Europe (Milo and Kahana, 2010). Ireland has long been recognised as being a high risk area for MS, in part due to the seminal research of Allison and Millar in the 1950s and prevalence rates here have been reported as being from 73 per 100,000 to as high as 290.3/100,000 in Co. Donegal [1] (Brady et al., 1977, Lonergan et al., 2011, Allison and Millar, 1954, McGuigan et al., 2004) (see Table 9). We estimate that there is approximately 9,000 people living with MS in Ireland and recent evidence finds an annual incidence rate of 5.97 per 100,000, which approximates to 290 new cases being diagnosed with MS in Ireland, annually (K. O'Connell 2015)

Due to the early onset of the condition and indeed its long duration, MS impacts heavily on the lives of those with the condition. As a consequence of relapses and symptoms of MS, hospitalisations are commonplace, resulting in the disruption of work, social and family life. The employment-related consequences of MS are well documented with very high levels of absenteeism, presenteeism and permanent withdrawal from the workforce due to MS, commonly being reported (Kobelt et al., 2006b, Karampampa et al., 2012a, Taylor et al., 2007). This restriction in professional activities allied with symptoms such as weakness, fatigue and cognitive impairment can lead to depression and isolation, further impinging on the quality of life (QoL) of those with the condition (L. Ford, 2001). Lifetime prevalence estimates of depression in people with MS are high, typically falling around 50% –more than twofold of that experienced in the general population (Arnett and Randolph, 2006, Horwath et al., 1992).

While it is clear that MS has a tremendous impact on the lives of those with the condition, the same is also true for their family members. During relapses and as the disease course progresses, a family member, in many cases a spouse, is required to adapt their lives to cope with the caregiving responsibilities associated with MS. Reduced working weeks and indeed having to permanently withdraw from the workforce are also commonplace for those who care for people with MS (Kobelt et al., 2006b, Karampampa et al., 2012a). Furthermore, the caregiving experience can be both physically and psychologically demanding and consequently may lead to a deterioration of physical and mental health, further increasing the caregving burden (Brouwer, van Exel et al. 2005).

As the onset of MS typically occurs early in adult life, people are affected during their most productive years – this statement rings true for those with the condition and to a degree their family members. As a consequence of this and allied with the well documented

large direct medical costs associated with the condition, MS has a considerable associated economic cost. The economic cost of MS has been studied in several countries (see Chapter 3), until recently no such studies were undertaken in an Irish context, however in 2014 two studies were published: (Fogarty et al., 2014, O'Connell et al., 2014).

The aim of this report therefore is to add to the existing international MS literature; to assess whether the results of nationwide and web-based survey corresponds with a clinic-bases survey; to enrich the information base with respect to Irish research, in particular to estimate the economic costs of MS based on a nationally representative sample. With this aim in mind, MS Ireland invited people with MS, living in Ireland, to complete a questionnaire to capture the costs of MS. This cross-sectional, self-reported survey was available online for one month in early 2015, and paper questionnaires were made available for those who did not have access to the internet and wished to participate.

Using such a survey based study, facilitates a "bottom up" approach,[2] which will provide estimates of the direct costs (i.e., the medical costs directly related to MS); the indirect costs (i.e., costs arising to the individual or society as a result of MS –e.g., ability to work); and lastly intangible costs (i.e., the costs that can be attributed to 'goods' for which there is no market yet but where there is a willingness to pay, such as disability). In estimating these three costs categories, it is the aim of this report to provide a comprehensive assessment of the societal costs of multiple sclerosis in Ireland.

1. For a discussion on the geographical variation in MS prevalence, see Chapter 5: Epidemiology of MS in Ireland.
2. This research can therefore be categorised as a descriptive cost of illness study using 'bottom up' data collection strategies where costs are estimated in a sample of people with MS and extrapolated to the national level.

My MS Story

"Support from the sidelines"

I was young, just finished college and I was fit and ready to start with my life ahead. It was something I never thought I'd have to deal with at such a young age. I had played rugby in school and college and was super fit. Because of my sporting activity I was physically very strong and active. I also had a great social life built around it. Being diagnosed with MS took away one of my passions.

In 2005 I was in Australia with friends and while doing sprints one day, I just fell over. Back in Ireland later that year my sight went blurry in my left eye. I went back to college but I was tired and felt uncoordinated.

In 2006 I was diagnosed with MS. At the time I was shocked. I had no idea what MS was but had thought it was something older people got. I also thought because I was young and active that I shouldn't have any health worries. On being diagnosed, because I didn't know much about multiple sclerosis or research so much, it wasn't too bad for me.

However, over the years it has probably affected me more as my body and abilities have changed and I've had to face my MS. The first two years were bad, health-wise. I had a number of relapses and struggled to come to terms with it all. I have been relapse free for four years but I still get headaches, dizziness and tiredness. But I've learned to spot triggers that may make things worse and I've definitely learned to deal with problems.

I do get down sometime but I try to get on with things and not dwell. I think it's really important to talk openly and honestly to people – friends, family and others with MS. You need a support network and these relationships will help get you through the tough times. One of the greatest gifts for me is to have a sense of humour; it helps me see the bigger picture that is my life.

Gareth, Dublin

3. Review of the International Literature

3.1 Introduction

The economic burden MS can impose on the person with the condition, and on society, has been widely researched internationally. While these studies have generated differing results, what cannot be denied is the substantial economic cost of MS. As can be seen in Table 4, in all of the studies examined in this literature review, MS imposes an excess economic burden. This burden ranges from as low as a €22,486 total mean annual cost per person with MS in France according to Karampampa et al. (2012), to a high of €84,384 total mean annual cost per person in Norway (Svendsen et al., 2012) (all costs inflated to € 2014)[3].

Table 1. Cost of MS – Review of the literature

Country	Primary Author	Year	Total mean annual cost €2014
UK	Kobelt	2000	€35,280
UK	Kobelt	2006	€43,973
Germany	Kobelt	2006	€47,111
Germany	Karampampa	2012	€45,311
France	Karampampa	2012	€22,486
Spain	Kobelt	2006	€40,081
Spain	Karampampa	2012	€31,879
Italy	Kobelt	2006	€31,758
Norway	Svendsen	2002	€84,384
US	Kobelt	2006	€51,162
Canada	Karampampa	2012	€27,580
Australia	Taylor	2007	€26,870
Netherlands	Kobelt	2006	€35, 883

Of course caution is advised when comparing results from different studies. Not only do methodologies differ, costs included and prices used often differ between the studies listed in Table 1. Furthermore, healthcare utilisation is quite variable across countries. Despite this, common themes clearly emerge that shed light on the nature of MS burden and the potential factors driving cost. A discussion of these themes is provided below.

3.2 The relationship between disability severity and costs

Table 1 above provides an overview of the total annual cost of MS for the average person with MS. Focusing on the mean cost however, overshadows the key findings of the literature: that the total cost of MS differs greatly depending on whether the severity of MS is 'mild', 'moderate' or 'severe'.

Various researchers (Kobelt et al., 2006b, Karampampa et al., 2012a, Fogarty et al., 2014, McCrone et al., 2008, Murphy et al., 1998) have found a clear correlation between costs and disability severity. Disability severity is often most frequently measured by the 'Expanded Disability Status Scale' (EDSS) instrument that measures disability level based on the level of ambulation. According to this scale, an EDSS score less than 3 is equated with having minimal or 'mild' disability, and EDSS score between 4 and 6.5 is equated with having 'moderate' disability and an EDSS of over 7 is equated with one having 'severe' disability.

Kobelt et al. (2006) carried out the largest cross-country study on burden of illness to date. It was conducted on people with multiple sclerosis in nine countries (Austria; Italy; Spain; Sweden; Switzerland; the UK; Belgium; Germany and the Netherlands) using the same cost methodology. A sample of 13,286 people with MS participated. Unsurprisingly, in all of the countries studies, higher costs were

3. Costs were inflated to 2014 prices using Consumer Price Indices specific to each country and subsequently converted into Euro values, where necessary

found for participants with higher levels of disability. The total mean annual cost per person with MS in these countries (adjusted for purchasing power) was estimated at €18,000 for mild disability, €36,500 for moderate disability and €62,000 for severe disability.

In the DEFENSE study by Ruutiainen et al. (2015), a similar pattern emerged, where the mean total annual cost of MS was €46,994, which increased with advancing disability from €10,835 (mild) to €109,901 for those with severe MS.

The TRIBUNE study by Karampampa et al. (2012) is a more recent cross-country cost of MS study. Karampampa (2012) estimated the burden of MS in France, Germany, Italy, Spain the UK and Canada. A common finding from the participating European countries was that both direct and indirect costs increased with disability severity. As is seen in the table below there is a strong positive relationship between EDSS scores and costs.

Table 2. Costs increasing with EDSS score (Karampampa et al., 2012)

EDSS score	Range of costs across countries
EDSS ≤ 3	€13,534 to €22,461
EDSS 4-6.5	€28,524 to €43,948
EDSS ≥ 7	€39, 592 to €65,395

The fact that people with MS with higher disability experience higher costs is well validated, not only found to be the case in these large multinational studies, but in national cost of MS studies in Ireland (Fogarty et al., 2014), the UK (McCrone et al., 2008), Norway (Svedsen et al., 2007) Australia (Taylor et al., 2007), the US (Kobelt et al., 2006a) and Canada (Karampampa et al., 2012b).

3.3 Indirect costs often outweigh direct healthcare costs

With regard to estimating the economic or societal cost of an illness, costs are usually broken down to two categories. 'Direct costs' refer to the costs that directly result from having an illness, for example the costs of hospitalisation, the cost of treatment and the cost of medical aids. Indirect costs, on the other hand, refer to costs that occur indirectly because of the illness, for example productivity losses as a result of the impact the illness has on your productivity and the impact the illness has on the caregiver.

While there is no denying that direct medical costs and in particular hospitalisation and disease modifying treatment is a large expense for the individual and for society, an interesting theme that has emerged from the literature is that in the case of MS indirect costs often outweigh direct costs. As can be seen from the below table in the majority of studies that provided a breakdown of their costs, indirect costs dominated direct costs, as a proportion of total cost. On average the relationship was as follows: 45% of total costs were direct costs while 55% of total costs were indirect costs. This can be seen in the pie chart below. A key reason for this is the impact MS has on the person's ability to work, and their need for informal care and supports. A further exploration is provided below.

Figure 1. Average relationship between direct and indirect costs in MS

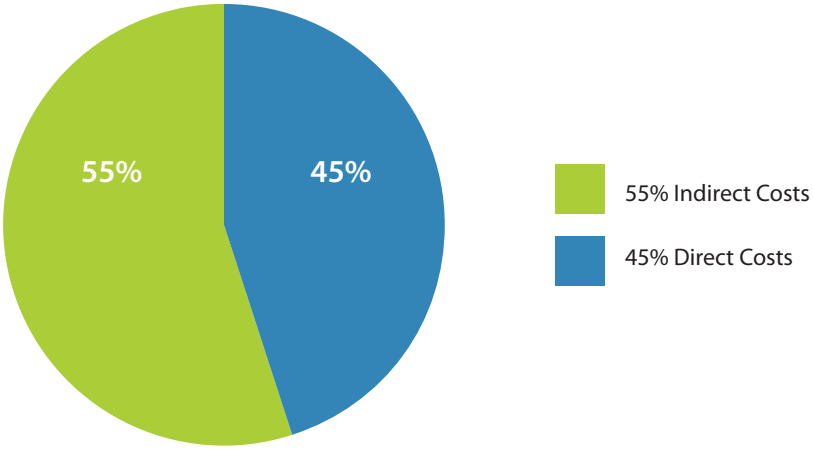


Table 3. Direct vs Indirect costs by country

Country	Author	Year	Direct vs Indirect
Ireland	Fogarty	2014	45% vs 55%
UK	McCrone	2008	28% vs 72%
UK	Kobelt	2000	28% vs 72%
Germany	Kobelt	2006	47% vs 53%
France	Karampampa	2006	85% vs 15%
Spain	Kobelt	2012	42% vs 56%
Norway	Svendsen	2006	39% vs 61%
Canada	Karampampa	2012	46% vs 64%
Australia	Taylor	2007	57% vs 43%
Netherlands	Kobelt	2006	42% vs 58%
Finland	Ruutiainen	2015	35% vs 65%

3.4 Impact MS has on ability to work

MS is associated with profound productivity losses for a variety of reasons. Since the average age of onset is between 20-40 years, MS impacts people at the prime of their working life. Furthermore, for those who experience relapses, or are unable to walk, or who experience extreme fatigue, it can be difficult to sustain a normal working life.

This unfortunate circumstance is reflected in the results of the reviewed studies. The proportion of the participants (N ≈13,286) in the Kobelt (2006) European study who worked was low, ranging between 25-40%. This statistic is notably lower than the employment rate (employment to population ratio of 15-64 year olds) in the 28 EU countries in 2013, which was 64.3% in 2006 the year of Kobelt's study (Eurostat., 2014). Similarly, 37% of European participants in the multinational TRIBUNE study were not employed at the time of the study as was 54% of Canadian participants in the Canadian arm of the TRIBUNE study, 50% of Norwegian participants in the Svendsen et al. (2007) study and 36% of those in the Finnish Ruutiainen et al. (2015) study. Again, the proportion of people with MS who are not employed is significantly higher than the total EU 28 working age population; the unemployment rate for the EU 28 has ranged between 6.1% in 2007 to 9.5% in 2013 (Eurostat, 2014b). In a similar manner, having to permanently withdraw from the workforce is a notable characteristic of the MS population. Significantly, 35% of UK participants in McCrone et al. (2008) under 65 were in early retirement, as was 50% in the Norwegian study, 45% in the Austrian and Dutch arm of the Kobelt (2006) study and more than half of the people with MS (56%), in the recent Finnish study (Ruutiainen et al., 2015)

As one can imagine, the ability to work is heavily dependent on the level of disability severity a person with MS experienced. In the Kobelt (2006) European study 70-80% of people with MS who had minimal disability (EDSS 0.0-1.0) were employed; however this percentage drops precipitously with increasing disability. At an EDSS level of 3.0, a level of disability that is not associated with loss of independence, close to 50% of people with MS are unemployed (Giovannoni, 2013). Furthermore, this rate is dramatically lower for people with very severe MS with only 10% of people with MS with EDSS 8.0-9.0 in employment. In a similar vein, results from the multinational TRIBUNE study and Murphy et al's (1998) European studies showed that the percentage of people with MS that were retired due to MS increased with advancing disability severity. Professor Gavin Giovannoni suspects that the reason MS has such a profound effect on labour force participation, is due to the cognitive impairment which can be a consequence of MS, and the comorbidities of fatigue, depression and anxiety that are associated with the condition[4].

With this in mind, it is easily understood why total costs increase with increasing disability severity, although it must be noted that this cost component usually is the highest in the 'moderate' subgroup as this is where the impact of MS on work kicks in (Fogarty et al, 2014).

For people with MS who are in employment, the evidence implies that good proportions are unable to maintain the same working hours as the average healthy worker. Approximately 50% of people with MS in the Kobelt (2006) study indicated that they had to reduce the number of hours worked or change their type of work. McCrone (2008) also noted the impact MS has on day to day

4. In the 2012 paper by Giovannoni, Foley and Brandes on the hidden disabilities in MS, the authors draw attention to the interesting statistics on the impact of MS on employment. They refer to the fact that two thirds of people with MS are unable to maintain employment (135). They state that specific symptoms such as fatigue and cognitive performance have been associated with increased odds of becoming unemployed (133). For example they refer to one study which showed that 90% of people with MS who reduced their working hours reported that fatigue was responsible for this change (78). The severity of depression has also been correlated to unemployment (135)

productivity; 4% of their UK participants had days off work because of illness and 7.7% of their UK participants had to reduce their working hours. Likewise, 14% of the participants in the Norwegian study (Svendsen et al., 2008) had reduced posts, of which the average reduction in work load was 51.5%.

With these effects of MS on ability to work in mind, Kobelt et al. (2006) come to the conclusion that productivity losses represent the single highest contributor to societal costs. Indeed, in Ruutiainen et al. (2015), productivity losses constituted some 44% of the total costs. While in Svendsen et al. (2012), the annual cost of productivity losses to Norwegian society was €267,588,000, equal to 61% of total societal cost of MS.

3.5 Informal caregiving

Informal caregivers, by definition, are not generally paid yet there is a cost to themselves and society for their time. The cost of informal caregiving, according to the literature, would be the second reason why indirect costs escalate above direct costs[5].

The 1998 study 'Economic Evaluation of Multiple Sclerosis in the UK, Germany and France' by Murphy et al, drew particular attention to the fact that informal care can be a substantial cost driver. They found that despite the fact that the UK had lower medical costs than Germany and France the reliance on informal caregivers as a means of support in the UK, led the UK to have the highest total annual costs compared to the other two European countries. Caregiving costs alone accounted for 71, 70 and 64% of all non-medical costs in mild moderate and severe MS subgroups in the UK respectively.

Kobelt (2006) also focused on the significance of informal care as a cost driver. This study found that the UK and Sweden had the highest costs particularly in advanced disease, out of the nine countries that participated in this study, and explained that the UK had the highest costs owing to the high use of informal care. Approximately 62% of respondents in the UK required informal care. Consequently 31% of the total mean annual cost of MS per respondent was generated from the use of informal care.

Likewise, using the same methodology and valuing technique, 30% of total annual cost of MS per person in Spain was generated from informal care costs. However this value was much lower for Finland, The Netherlands and the UK, which amounted to 13%, 12% and 11% of total costs respectively.

These differing results point to the fact that cultural factors are highly influential in determining whether informal care is prominent in society, and hence a significant cost driver. Kobelt et al. (2006) suggest that *'The amount of informal care is generally a function of the extent of services offered by the healthcare systems. A good example of this is Sweden, where 'people with MS' with severe disability have access to personal assistants who are funded by the system'.*

The sizable influence informal care has on total cost is a common theme in the reviewed literature, and has been discussed in (Kobelt et al., 2006; Karampampa et al., 2012 Murphy et al, 1998; McCrone et al., 2008).[6] The prominence of informal care as the main form of care and support for people with MS has increased in recent years, as a result of the recession that has affected many countries and the resulting actions of some governments. Austerity measures have reduced national health budgets, and as a result there is often less care and support available publicly for people with MS which means this role, and this cost, is shifted to the informal caregiver. Thus the burden on informal caregivers is a burning and concerning issue of late, and may receive more attention in the literature in the future.

3.6 The impact of an MS relapse on cost in RRMS

Reviewing the literature on the cost of MS revealed the significant cost that can entail from having a relapse. As is well known, relapses are a characteristic for a sizable proportion of those with MS, particularly those who have 'Relapsing Remitting Multiple Sclerosis' (RRMS). Relapsing-remitting MS (RRMS) is the most common form of MS, with approximately 80-85% of all people with MS experiencing a relapsing–remitting (RR) onset of the disease. RRMS is characterised by unpredictable acute attacks (known as relapses) accompanied by worsening of symptoms or the appearance of new symptoms, followed by periods of remission during which there may be a full or partial recovery from the trauma of the relapse (Raimundo et al., 2013)

The results of the analysed studies show that there is a substantial proportion of participants had experienced a relapse recently;

5. Please note that while some studies classify informal care as an indirect cost , other studies often classify informal care as a 'direct non-medical cost'. For the purposes of this study informal care will be classified as an indirect cost.

6. It must be borne in mind that huge differences in the cost of informal caregiving can result from the way in which one values caregiving; whether it is valued based on productivity of the working caregiver or valued based on the loss of leisure time of the working and non-working informal caregiver, can generate highly different results. Thus an in-depth analysis of the cost of informal caregiving across the studies is not worthwhile, but an overview of the importance of informal caregiving as a cost driver is more valuable. We will return to this issue of the different methods of valuing informal care in chapter three.

between 16 and 29% of respondents in the large European Kobelt study had experienced a relapse in the preceding three months to the questionnaire. Similarly 14.3% of respondents (of EDSS 5.5 or lower) had experienced a relapse in the preceding month to the questionnaire in the Norwegian study (Svendsen et al., 2012).

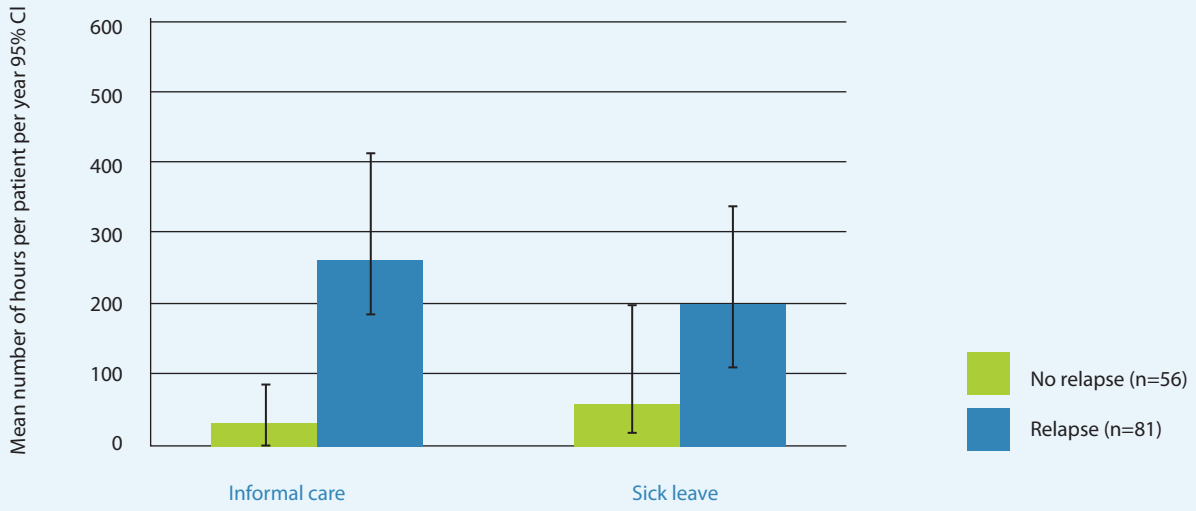
Typically in the literature, the mean cost of a relapse is estimated by calculating the difference in costs between those who have the same level of disability (EDSS 5.0 or below), who had experienced a relapse (in a stated recall period) versus those who had not experienced a relapse. **This excess cost attributable to a relapse**, generally ranged between €3,270 and €4,670 in most of the European countries in the Kobelt et al. (2006) study. This cost was, however, significantly higher in Austria, equating to €6,740. The Karampampa et al. (2012), multinational study, also found that a relapse amounted to a similar cost, ranging between €4,751 and €6,625 across the European countries in their studies. In the Canadian arm of the TRIBUNE study by Karampampa et al. (2012) the additional cost of a relapse was found to be higher at €7,692. While in the recent Finnish study, the authors estimated total cost per relapse as being €9,778 (Ruutiainen et al., 2015).

In the Norwegian cost of MS study (Svendsen et al., 2012) the researchers found, that assuming a relapse lasts for two months on average, the cost of a relapse was estimated at €6,450. Thus, the average approximate cost of a relapse in the international research ranges from €3,270 to €9,778

However, as with the total cost of MS, the cost of a relapse is related to the levels of disability severity. Karampampa et al. (2012) found that the excess cost of a relapse depended on the severity of a relapse, with relapses that required steroid treatments or hospitalization resulting in higher costs compared to subgroups that did not require such treatment. The Canadian study found that people with MS who experience severe relapses requiring hospitalisation having nearly twice as a high a cost compared to those whose relapse required no hospitalisation (€14,640 versus €7,692).

The TRIBUNE study by Karampampa et al. (2012) provided an analysis into why relapses entailed an additional cost. People with RRMS who experienced at least one relapse in the previous 12 months had higher disability compared to the same subgroup of those without a relapse (p-values <0.05 in France, Germany and Spain). Other studies have informed us that disability is a significant predictor of ability to work (Kobelt et al., 2006, Fogarty et al., 2014), thus a potential reason for the cost of a relapse is the impact a relapse has on ability to work. The impact a relapse has on the need for informal caregiving is another potential factor, as highlighted in the Canadian arm of the Tribune study. A striking difference was found between the hours of informal care and sick leave needed between those with non-relapsing RRMS (49 hours informal care and 48 hours of sick leave) and the hours of informal care and sick leave of those within this subgroup who reported experiencing at least one relapse (259 hours of informal care and 211 hours of sick leave).

Table 4. Mean annual hours of informal care and sick leave according to relapse status



Source: Karampampa et al (2012b)

3.7 The impact of MS on Quality of Life

We have thus far spoken of the impact MS has on the costs to the person with MS, and to society. However MS imposes a burden on the person with MS through the impact MS has on their quality of life. While we will delve into deeper detail on how loss of quality of life is measured, valued, and attributed a cost in Chapter 5, it is essential to note that a common theme that has emerged from the literature is the undeniable impact MS has on quality of life (QoL). A striking finding from the European cost of MS study by Kobelt et al. (2006) was that, unlike costs, utility scores measure quality of life, were virtually the same across countries. This confirms the overwhelming effect of QoL on MS, but is obviously also the consequence of the same health state tariff for the utility instrument (EQ-5D) was used.

As one would expect, higher levels of disability severity is associated with lower levels of quality of life. This finding is replicated in a plethora of cost of MS studies. Kobelt (2006) *remarkably show that while utility scores were relatively high for respondents with EDSS score of 2.0 (0.70), this score was significantly lower for those with higher levels of disability at an EDSS level of 6.5 (0.45).* These authors found that the utility loss due to multiple sclerosis translated into a mean QALY loss of 0.27 per respondent and an intangible cost[7] of €13,400 (assuming a willingness to pay for a QALY of €50,000).

Similarly, people with MS who experience relapses also display diminished quality of life compared to those who have MS, but are relapse free. This is commonly reported in the literature (Karampampa et al., 2012; Kobelt et al., 2006; Svendsen et al., 2012; Henriksson et al., 2001). Kobelt et al. (2006) established that having a relapse was associated with a utility loss of 0.1 across countries (as measured by the EQ-5D[8])

3.8 Summary

There is ample evidence to support the view that MS is associated with a substantial- economic burden, for the person with MS and for society in general. Despite the fact that the international results on the cost of MS have been generated using different methodology, cost components and unit prices to name only some potential differences, certain striking commonalities or stylized facts have emerged from this literature review. The international findings suggest that the total mean average annual cost of MS is substantial, and depends on the level of disability severity. Indirect costs are generally higher than direct costs, owing to the substantial impact MS has on one's ability to work and their dependence on informal care. Those who experience relapses have higher costs per year and finally, the last common theme is the clear impact MS has on quality life with a clear negative relationship between disability severity and utility scores. Our study will examine whether such common themes will be evident in the results from those who have participated in this national questionnaire on 'The Societal Cost of MS in Ireland'.

7. Kobelt et al (2006) define intangible costs as costs due to pain, grief, anxiety and social handicap.

8. EQ-5D is a standardized instrument for use as a generic measure of the quality of health-related life and of health outcome. It is particularly associated with the QALY (quality-adjusted life-year). It is designed for self-completion by respondents and is suited for use in postal surveys, clinics and face-to-face interviews. The EQ-5D has five dimensions: Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/Depression. The traditional EQ-5D instrument described each dimension in terms of three levels: 1- no problem, 2 - some problem, 3 - extreme problem. In each case, the instrument comprises two parts: respondents rate their health on the dimensions/levels and record an overall assessment of their health on a visual analogue scale, the EQ-VAS.

My MS Story

"Life must go on"

Having lived and worked in Canada, in 2001 I returned to County Offaly to work in the family business. One night, whilst working away at home, I experienced an unbelievable headache, pins and needles and a numb feeling all across the left side of my body. I asked my brother to take me into the hospital where I was kept in for the next four weeks. Between the poking and pulling, I had two lumber taps, numerous blood tests and a MRI scan. I will never forget that Wednesday afternoon when the curtains were drawn around my bed. The doctor told me I had MS. I know he told me all the technical detail but, at thattime, I might as well have been told I had days to live. I was in utter shock.

After leaving hospital, I dove straight into sourcing as much Information as possible about the new title in my life; Relapse Remitting MS. People ask what has kept me going over the past number of years and I have to say it has been the people I have met since becoming involved with MS Ireland.

Has this shadow of a disease stopped me in any way? No. I have never let it stop me getting on with my life. I am a skilled volunteer First Aider with the Civil Defence, I help out with local meals and wheels and I also volunteer with my local voluntary Branch of MS Ireland. As well as this, I work part-time as a youth worker.

Sure I get down sometimes. I have had five relapses in nine years. I feel like not getting out of bed some days due to headaches or tiredness. But, life must go on. I owe a lot to the new people in my life, both MS friends and non MS friends. As I always say, if I can make one person smile today I am doing well.

Austin Dempsey, Offaly

4. Review of Existing Irish Studies

The academic literature on the economic burden of MS in the Republic of Ireland has been relatively sparse. Before 2014 the majority of the literature focused on the prevalence of MS in Ireland, investigating the hypothesis of whether latitudinal variation existed in the prevalence of MS across Ireland and the potential reasons for this (2011, Gray et al., 2008, McGuigan et al., 2004).[9] In 2014 however, two publications on the economic cost of MS in Ireland were published (Fogarty et al., 2014, O'Connell et al., 2014)

The first publication was the 'Direct and Indirect Economic Consequences of Multiple Sclerosis in Ireland' by Fogarty et al. (2014). The findings of Fogarty's study provides key insights into the nature of the economic costs of MS in Ireland. A relatively small sample of 214 people with MS were recruited by neurologists in a tertiary referral, specialist MS outpatient clinic in South Dublin, who were then subsequently interviewed.

The results from the study provide key figures depicting the burden of MS. For example, Fogarty et al. (2014), found that as disease progresses from the mild to moderate stage, a significant reduction in employment ensues from 54.4% to 23.2%. Connected to this, the mean age at retirement of people with MS in this sample was relatively young at 44.3 years and MS related sick leave/reduction in hours was taken by 32.6% of those in paid employment.

Similar to the international literature is Fogarty's finding of the strong relationship between disability and quality of life, with quality of life or 'utility' scores as measured by the EQ-5D-5L falling as disability (EDSS) scores increased.

Of particular interest, Fogarty et al. (2014) highlighted the composition of costs of MS in Ireland. They found, consistent with international findings, that costs increase with increasing disability, as can be seen in Table 1 below. The researchers highlight the extremity of the relationship between disability severity and costs, stating that mean annual direct costs increased more than fourfold from €12,822 to €55,900 per person from moderate to severe disability driven by the excess cost of institutional care and provision of professional care in the home.

Table 5. Breakdown of costs by MS severity (Fogarty et al., 2014)

	Mild	Mod	Severe
Total direct medical	€ 10,110	€9,064	€27,745
Hospital/rehabilitation	€85	€1,187	€8,475
Outpatient/primary care	€632	€1,710	€2,451
Long-term care	€0	€847	€13,378
Lab/rad/investigations	€311	€265	€159
Medication	€8,313	€5,054	€3,251
Total direct non-medical	€209	€4,072	€29,210
Aids and adaptations	€62	€1,579	€2,795
Professional home help	€148	€2,493	€26,415
Total direct costs	€10,321	€13,136	€56,924
Informal care	€826	€9,953	€18,200
Productivity losses	€8,687	€22,076	€21,517
Total indirect costs	€9,513	€32,029	€39,716

9. For a discussion on MS prevalence in Ireland, see Chapter 5: Epidemiology of MS in Ireland

Interestingly, the authors draw attention to the fact that cost compositions change between the three different EDSS groups. As disability increases (from mild to moderate) indirect costs become a bigger cost component owing to the substantial productivity losses and the more intense management needed. However, there is not much of an increase in productivity losses moving from the moderate to severe disability stages as the shift from employment occurs earlier on in the disease course, according to the authors. It can also be seen that there is a clear gradient between the dependence on informal care and the level of disability severity (9.6% mild, 54.2% of moderate and 92.9% of severe respondents received regular home help by family or a professional). This changing cost composition can be seen in Table 1.

This paper also provided useful detail on the use of disease modifying therapies (DMTs) in Ireland, previously relatively unknown. In their sample of 214 people with MS who attended this specialist clinic, Disease Modifying Therapies (DMTs) were prescribed for 61.4% and 29.6% of those with mild and moderate disability respectively. Subsequently, DMTs accounted for 76.1% of direct costs for those with mild disability and 29.6% of direct costs for those with moderate disability. However it must be noted that sample bias may be present here, with people with MS who require intense disease management and the use of DMTs more likely to attend neurological clinics, thus the DMT use and cost due to DMTs may be overestimated relative to the national average.

Extrapolating the results from this study to the Irish population, the Fogarty (2014) study estimated that the national annual direct and indirect costs are €127.8 (46%) and €149.6 million (54%) respectively resulting in a figure of €277.4 million for the total annual cost of MS in Ireland. They also conclude that that interventions that reduce disability progression and support working and living independently would reduce the overall cost of MS.

There are some limitations of the Fogarty et al (2014) study, which must be noted when analysing the results. The authors note that as the sample was recruited from one specialist MS outpatient clinic in Dublin only (albeit representing a geographical spread of people from several counties), the sample is slightly biased towards those early in the disease course. In an analysis of the representativeness of the sample, the authors state that *"In contrast to population studies that typically show peak distributions at EDSS 3 and 6, a peak in their cohort was observed at EDSS 1, reflecting a bias towards those early in the disease course.'* Thus how nationally representative these results are is questionable, which adds some doubt to the external validity of the study.

Furthermore Fogarty's estimation of the cost of MS may be undervalued. Firstly they do not estimate the additional cost that a relapse of MS can impose on the person with MS , which the O'Connell et al. (2014) paper has shown as being significant. Secondly, and with respect to the cost of informal care, lost leisure time of informal caregivers was not taken into account, and the hours of care giving provided by family and friends was capped at a maximum equivalent to the average number of working hours per week.

We build on the results of Fogarty et al. (2014) and in particular provide an estimate of the cost of an MS relapse, a more in-depth analysis of the indirect costs of MS such as care giving, and a deeper analysis of the impact of MS on QoL. The results from our national questionnaire should complement the results of Fogarty's single centre interview study.

A second single-centre study from a University Hospital in Dublin was published in 2014. O'Connell et al. (2014), examined the 'Economic Costs Associated with an MS Relapse'. The study design was that of a prospective audit over 18 months comprised of a medical chart review and questionnaire. The high cost that a relapse of MS can entail, and the desire to reduce the escalation of relapses is evident from the results of this study.

Relapses were classified according to the intensity of the relapse with regards to the level of medical services used, following the typology of O'Brien et al. (2003). Low intensity relapses were defined as requiring symptomatic management or a short course of oral steroids, moderate relapses were treated with intravenous steroids, and high intensity relapses required hospitalisation. It can be seen from Table 6 below that the cost of a relapse depends on the severity of the relapse, with costs increasing with severity.

Table 6. Cost of relapses according to relapse severity (O'Connell et al., 2014)

	Low Intensity	Moderate Intensity	High Intensity
Direct Costs	79%	69%	61%
Indirect Costs	21%	31%	39%
Total Cost	€503	€1,395	€8,862

The different forms of costs of a relapse can be seen in Table 7. Direct costs were collected from the neurologist while indirect costs were collected through a questionnaire given to the person with MS. It can be seen that radiology and MRI tests are quite expensive and hence a substantial component of the estimated cost of MS across the different subgroups in this study. Inpatient costs are the main driver of costs of high intensity relapses.

It must be noted that there are certain question marks over the estimates of the indirect costs. Only productivity losses of those employed are taken into account however MS is known to be associated with a low employment rate, and high early retirement rate. In this study, those who were unable to return to work following a relapse were only ascribed an 'economic' cost equal to disability payments during the year of the relapse. However in reality being unable to return work results in a lifetime of lost productivity and hence, substantial indirect costs. Furthermore the value of informal care is not included. As we will see from the large cost of MS studies carried out all over Europe by Kobelt et al. (2006b) and Karampampa et al. (2012a), O'Connell's estimation of indirect costs differs from the norm and hence it is plausible to conclude that the indirect costs of a relapse may be underestimated in this study.

Table 7. Cost components of relapses by severity levels (O'Connell et al., 2014)

	Low	Moderate	High
Direct Costs			
Contact MS Nurse Specialist	€23	€27	€14
Neurologist Review	€112	€145	€68
Other doctor review	€14	€0	€-
Medications	€8	€58	€443
Radiology	€238	€280	€164
Pathology	€8	€7	€168
Allied Health	€0	€0	€474
Day care	€0	€448	€0
Inpatient costs	€0	€0	€4,127
Indirect Costs	€0	€0	€0
Travel	€9	€35	€74
Parking	€1	€8	€34
Loss of earnings	€93	€321	€3,016
Disability	€0	€0	€691
Spouse's loss of earnings	€0	€77	€83
Childcare	€1	€5	€0
Meals	€0	€11	€36

The detrimental clinical impact of relapses was also highlighted in this report. The authors found a clear gradient between severity of relapse and disability progression. This study recorded that for those who experienced a high intensity relapse, the relapse increased the level of disability (mean 2.3 EDSS) during their relapse period compared to the low and moderate intensity group. Thus this study shows that there is considerable merit in reducing the number and severity relapses as they have consequences for disability progression as well as the resulting economic burden.

While O'Connell (2014) certainly provided useful detail on relapses, it must be noted that that the sample size of this study was small; the costs of 43 people with MS who experienced relapses were recorded. Because of this small sample size, there is great variability in the indirect costs across groups. Also, as with the Fogarty (2014) study, recruiting from a single specialist neurological centre in South Dublin means that the results may not be easily generalisable to the wider Irish population, and sample bias may be present as individuals who attend neurological clinics may differ in clinical profile to those who do not use this service. The authors state that this issue is particularly acute given the current variation of MS treatment options across Ireland; *'at present treatment patterns vary across Ireland as not all hospitals have a neurologist on site or the facilities to deliver steroids in an outpatient setting and so these findings only reflect the cost at a single specialist MS unit'.*

The aim of the MS Ireland study 'The Societal Cost of Multiple Sclerosis in Ireland' is to provide new Irish data on the cost of MS that is more broadly representative of the Irish MS population and provide robust evaluations on the direct, indirect and also the intangible costs of having MS and having an MS relapse. The methodology of well renowned 'cost of MS' studies that have been carried out worldwide: Kobelt et al. (2006b); Karampampa et al. (2012a) and Murphy et al. (1998) will be closely followed for comparability also.

My MS Story

"The dark days... they seem so long ago"

In March 2008 I was diagnosed with a very aggressive form of MS. For six years I had been living with symptoms such as upper limb weakness, pins and needles in my arms, disturbances in my vision and repetitive urinary tract infections. At one stage there werequeries over a brain tumor but as my working background had been as a hairdresser, the problem was put down to repetitive strain injury.

It was not until November 2007 when things took a drastic turn for the worst. I developed optic neuritis and developed an ataxic gait, a weakness in both legs and an increase in the severity in the symptoms. I had to give up my position in the salon I worked in. At my worst I had difficulty in doing almost anything independently.

Those were the dark days and thankfully, they seem so long ago. I have used exercise to bring myself back to independence. Through hard work and determination I achieved that goal and began walking again, which to me was an answered prayer. I now use a crutch when I'm out and about, pace myself with activities, use aids and appliances to help around the house and accept help from friends and family.

I now live the life of my choice not the life that was thrust upon me, and I live it to the best of my ability. It is not our disabilities that define us; but our abilities. Rehabilitation is an ongoing element to almost all people with MS. As I always say "What do we do when we fall? We pick ourselves up again".

Anne Marie Hayden, Roscommon

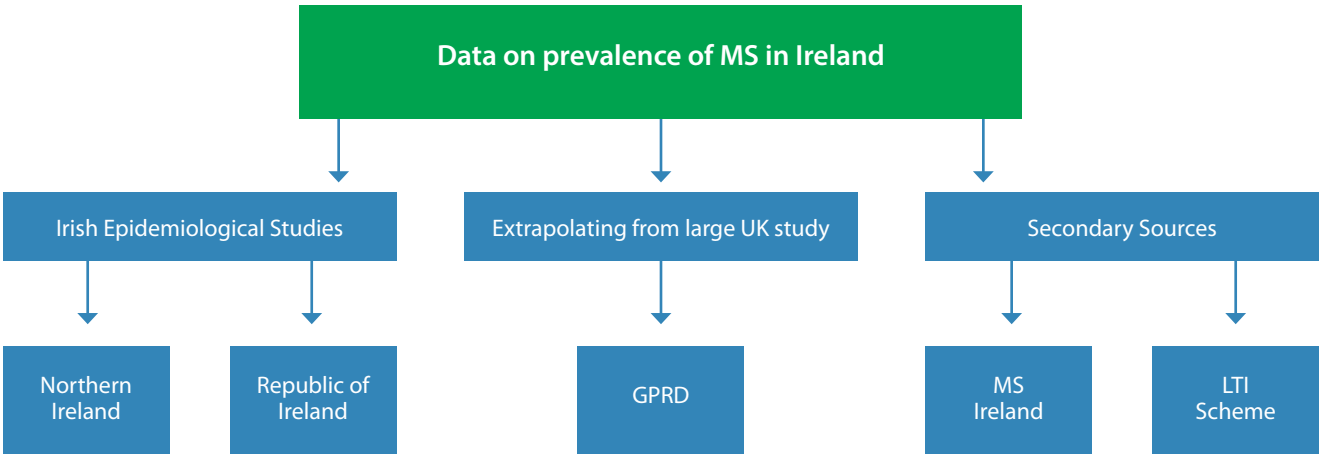
5. Epidemiology of MS in Ireland

5.1 Prevalence of Multiple Sclerosis in Ireland – Literature

A fundamental step in determining the economic impact of multiple sclerosis (MS) in a country is to identify the total number of people with MS residing in that country. This can be calculated from estimates of prevalence of MS in that country and the population of the country (global economic impact of multiple sclerosis).

Ireland does not have a national registry of people with MS, which makes the task of generating reliable statistics of prevalence difficult. The aim of this chapter is to outline the available information on the prevalence and incidence of MS in Ireland. Our approach to this chapter is set out below. Firstly the current literature on the prevalence of MS in Ireland will be reviewed. Secondly, findings from a large and reliable study on the epidemiology of MS in the UK will be extrapolated to the Irish population. Lastly, databases and secondary sources that have valuable information on the prevalence of MS in Ireland will be reviewed. This three pronged approach should provide a coherent picture of the epidemiology of MS in Ireland.

Figure 2. Prevalence of MS – Data source



5.2 Irish Studies

5.2.1 Northern Ireland

The geographical variation in MS prevalence has been of high interest to epidemiologists, neurologists and statisticians for over a century (McDonnell and Hawkins, 1998). Northern Ireland has been noted as a region with high prevalence of MS since the influential work of Allison and Miller in 1950. Consequently, Northern Ireland is one of the most surveyed populations for MS in the world (McDonnell and Hawkins, 1998). Owing to the proximity of the Republic of Ireland to Northern Ireland, and the plethora of literature on prevalence of MS in Northern Ireland, there is great merit in reviewing the epidemiological studies on MS from Northern Ireland.

The original, and most seminal, study on MS in Northern Ireland is from Allison and Millar (1954). This study was based on the population of Northern Ireland as a whole and all hospitals and doctors in the country were surveyed, and all people with MS availing of the services were individually assessed. Hence this was a highly extensive and ambitious study. Allison and Millar introduced a scheme of classifying people as 'probable MS', 'early MS', or 'possible MS', that is still widely used. They identified Northern Ireland as a **high risk area for MS**, observing prevalence rates of **51/100,000 in 1951** (population: 1,370,709) and **80 per 100,000 in 1961** (population: 1,484,775). MS was found to be more prevalent in females than males, with a prevalence ratio of 1.26:1 being found in their 1951 study. Furthermore, in 1951, Allison and Millar calculated incidence for the period 1937–1951. They found a mean annual incidence of 2.74/100,000 over this time, with a higher incidence in females (2.91/100,000/year) than males (2.56/100,000/year). In their follow-up study in 1961, incidence had increased to 4.4/100,000 (Allison and Millar, 1961). However it must be noted that these results may be undermined by certain methodological caveats[10], which implies that these results are underestimated.

Subsequent studies have shown higher prevalence rates of MS in Northern Ireland. A study of the distribution of MS in the north-east of Northern Ireland (Coleraine, Ballymoney and Moyle: population of 86,500) by Hawkins in 1987 produced a crude prevalence rate of 138/100,000.30. MS, in this case, was defined according to the Poser Criteria (McDonnell and Hawkins, 1998).

In 2000, Hawkins and McDonnell studied the north eastern region of Northern Ireland, with the addition of Ballymena (population 151,000). Hawkins and McDonnell (2000) restricted the sample of cases with MS in this region to only those who satisfy the Poser criteria of having 'definite' or 'probable' MS (n=254), which gave a prevalence rate of 168.2/100,000 (95% CI 147.5-188.9/100,000). Based on these figures and the presumption that there may be an even distribution of the disease across Northern Ireland, Hawkins and McDonnell (2000) position that almost 3,000 individuals in Northern Ireland have definite or probable MS and there are a further 400 suspected cases in the region as a whole. The authors state that this figure sadly confirmed that NI had one of the highest and rising MS prevalence rates in the world, implying an enormous potential for societal costs.

Furthermore, the study from this year provided interesting characteristics of this northern Irish sample. 35% of people who had RRMS, 12.9% benign disease, 39.6% had SPMS 12.5% had PPMS. Females predominated (ratio, 2.1: 1) and the average age at onset was 31.6 years. The spectrum of disability was broad and 20% could be considered to have relatively "benign" disability.

Gray, McDonnell and Hawkins (2008) also surveyed this north eastern region in Northern Ireland (population 160,446) in 2004, thus updating the figures from Hawkins and McDonnell (1996) study. In this instance the authors were interested in people with MS who had 'definite' or 'probable' MS as defined by the Poser criteria. Along with this the authors were also interested in the recently developed McDonald criteria that defined MS where individuals had evidence of lesions separated by space and time. The prevalence rate in this region in 2004 was much higher than the equivalent 1996 study. Including 370 cases with MS in a population of 160,446 results in a prevalence rate of 230.6/100,000 (95% CI 207.7–255.4) (Gray, McDonnell and Hawkins, 2008). There were 247 females and 123 males (ratio 2:1), the mean age of onset was relatively young at 32.6 years and the most common form of MS was RRMS (56.6%) followed by SPMS (36%) and PPMS (7.4%)

In this prevalence study, current study, the incidence was estimated for the year 1996. Incidence in 1996 was 9.3/100,000 with a higher incidence in females of 10.3/100,000/year than males of 8.3/100,000/year. This is significantly higher than the incidence rates found in the Allison and Millar studies and the higher incidence in females explains the increasing female to male prevalence ratio of 2:1 in this study compared with a prevalence ratio of 1.26:1 in Alison and Millar's study in 1952. The authors conclude that Northern Ireland is an area with high and rising prevalence for MS. While improved case ascertainment and earlier diagnosis may have contributed to this rise, they find that the evidence of the rise in incidence confirms a true increase of the disease (Gray, Hawkins and McDonnell, 2008). However some caution must be taken with assertions of increasing prevalence, as most epidemiological studies when repeated generally result in higher figures each time. This is a phenomenon seen worldwide.

10. Firstly, by the prevalence date replies had not been received from 25% of the doctors in Northern Ireland. Secondly, the incidence rate was calculated over a prolonged period and up to the prevalence date (1937-51) and may therefore have missed those who had onset of disease during this period but who died before the survey was carried out, and also those who had onset during this period but had not yet been identified (Hawkins and McDonnell, 2000).

5.2.2 Republic of Ireland

The literature on epidemiology of MS in the Republic of Ireland (ROI) had been relatively less detailed until the 1970's, however there has been one study per decade since that we will briefly outline. The first notable study was carried out by Brady et al. (1977). It involved the entire population of the ROI and generated an overall prevalence rate for individuals with probable or possible disease of 73/100,000. However, according to McGuigan et al. (2004), its findings were blighted by problems of case ascertainment that typically accompany studies with a large population of this size.

In 1984, Hutchinson studied the prevalence of MS, as defined by the McDonald criteria, in county Wexford. This study yielded a prevalence rate of 48.4/100,000 for progressive probable and clinically definite MS (Hutchinson, 1986). This low prevalence rate, and general findings of the study, was questioned as a remarkable 40% of the population had benign disease which indicated that there was perhaps a bias present in the case ascertainment against those with greater disability. (McDonnell and Hawkins, 2000; McGuigan et al., 2004)

In McGuigan et al. (2004), the authors compared the prevalence of MS in Wexford and Donegal, to establish whether a variation in MS exists within Ireland. Prevalence of MS was defined according to Poser's diagnostic criteria, of having 'clinically definite or probable MS' and if respondents were in the county borders in January 2001[11]. For county Wexford the prevalence rate was found to be **120.7/100,000** (95% CI: 100.6-143.8). The equivalent prevalence rate for Donegal in 2001 was 184.6/100,000 (95% ci- 162-209.5). Thus the prevalence in Donegal was found to be significantly higher than in Wexford (Z=3.84 p=<0.001). This study was underpowered to perform a comparison of incidence rates between the two counties, as it was designed as a prevalence study. The authors conclude that this striking result confirms that there is a latitudinal variation in the prevalence of MS in Ireland. However they state that this may not be due to latitudinal/environmental factors, rather it is more likely due to the prevalence of MS susceptibility genes in the background populations of the two regions.

In the 2004 paper by McGuigan et al, blood sample from the MS populations in Wexford and Donegal were taken, along with controls from both counties. The samples were tested (HLA typed) to see if they carried the DRB1*1501 and DQB1*0602 alleles, such genetic characteristics have been found in populations in Northern Europe such as Scotland which are associated with higher rates of MS. Although the numbers tested in this study was small, the Donegal sample control population also had a significantly higher carriage rate of the HLA DRB1*1501 – DQB1*0602 haplotype relative to the Wexford sample control population ($\chi 2=5.02$, $p \leq 0.05$,OR=1.616, CI 1.060–2.464, p=0.05).The researchers conclude that based on these results it is plausible that one of the factors accounting for the difference in MS prevalence across Ireland is likely to be variation in the genetic predisposition to MS within the Irish population (McGuigan et al., 2005).

In Lonergan et al. (2011), the authors investigated whether vitamin D influenced the risk of MS, and in doing so the researchers shed light on the prevalence of MS in Ireland. In this instance the prevalence of MS was calculated for Donegal (northern latitude) and Wexford (southern latitude); and one urban area: southeast Dublin city (intermediate latitude).

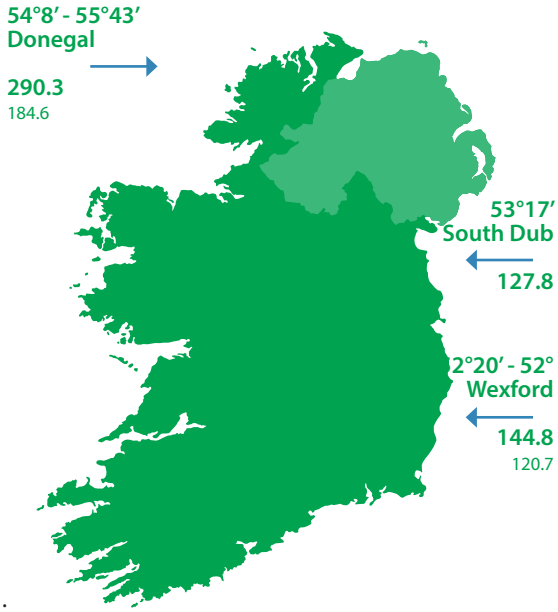
These researchers found that the MS prevalence on 31 December 2007 was: Donegal 290.3/105 (95% CI 238.7 to 255.5), Wexford 144.8/105 (95% CI 138.3 to 151.9) and southeast Dublin 127.8/105 (95% CI 131.6 to 146.7). Similar to the results reported in McGuigan et al. (2004), prevalence was significantly higher in Donegal than in Wexford (p <0.0001). The results of this 2011 study, in comparison to McGuigan et al. (2004), showed that prevalence in 2007 was significantly greater in Donegal (northwest) (290.3/105, 95% CI 262.3 to 321.7) compared with 2001 (184.6/105; 162 to 209.5). There was a non-significant increase in Wexford. Again, incidence could not be calculated in this study due to inability to ascertain year of (MS) onset data in all identified cases (Lonergan et al., 2011).

Table 8. Irish MS prevalence estimates (per 100,000)

Irish Prevalence Study	Prevalence Rate
Brady et al., (1977)	73
Hutchinson., (1984)	48.4
McGuigan et al., (2004)	152.65
Lonergan et al., (2011)	187.5

11. It must be noted that prevalence rates were based on pop of Northern Ireland from 1996 study to allow comparisons with McDonnell and Hawkins 1996 study of Northern Ireland.

Figure 3. Regional disparity of MS prevalence in Ireland (Lonergan et al, 2011)



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Recent research in the area has also found distinct regional differences with respect to the epidemiology of MS in Ireland. This time focussing on the incidence of MS, O'Connell et al. (2015) also find evidence of a latitudinal gradient and report an incidence rate for the northern counties of 9.6/100,000 compared to 5.1/100,000 for the southern counties. In total 292 people fulfilled the inclusion criteria, yielding an age-standardised incidence rate of 5.97/100,000.

5.2.3 Prevalence in Ireland – extrapolating from the UK

While there have been some epidemiological studies of MS in Ireland that have looked at the latitudinal variation of the disease, there is currently a lack of comprehensive information of the overall prevalence and incidence of MS in Ireland. In an attempt to overcome this information deficit, estimates from a large UK population based study on incidence and prevalence of MS were adopted and adapted to reflect the Irish setting. In Mackenzie et al. (2014) the authors used a large UK primary care database called the General Practice Research Database (GPRD).

This database, and hence results from this study, has many merits. The GPRD population included about 8% of the UK population in 2010, and their age and sex distributions were similar to those of the whole population (Mackenzie et al., 2014). The authors estimated that there were 126,669 people living with MS in the UK in 2010 (203.4 per 100 000 population) and that 6,003 new cases were diagnosed that year (9.64 per 100 000/year)[12].

12. For GPRD, Read codes for confirmed diagnoses of MS (ie, codes beginning F20) were used. For Hospital Episode Statistics (HES) the International Classification of Diseases (ICD10) code for MS (G35) was used. Incident cases were defined as the first occurrence of a code for MS if it occurred after the 2-year screening period.

Table 9. UK prevalence estimates (Mackenzie et al., 2013)

	Population	Prevalence / 10^5	Prevalent cases	Incidence / 10^5/year	Incident cases
Total UK	62,262,300	203.4	126,699	9.64	6,003
England	52,233,900	199.2	104,451	9.08	4,745
Wales	3,006,300	168	5,052	7.92	238
Scotland	5,222,300	255.2	13,328	15.29	798
Northern Ireland	1,799,800	213.2	3,838	12.25	221

As a breakdown by age and by sex was available in this study, it was possible to adjust the prevalence rates to the Irish age and sex profile, consistent with most recent Irish census figures. Doing so provided for an estimate of 0.2% for Ireland. According to this estimate we might reasonably expect there to be 9,308 people living with MS in Ireland (Table 1).

Figure 4. Prevalence of MS – UK and Ireland

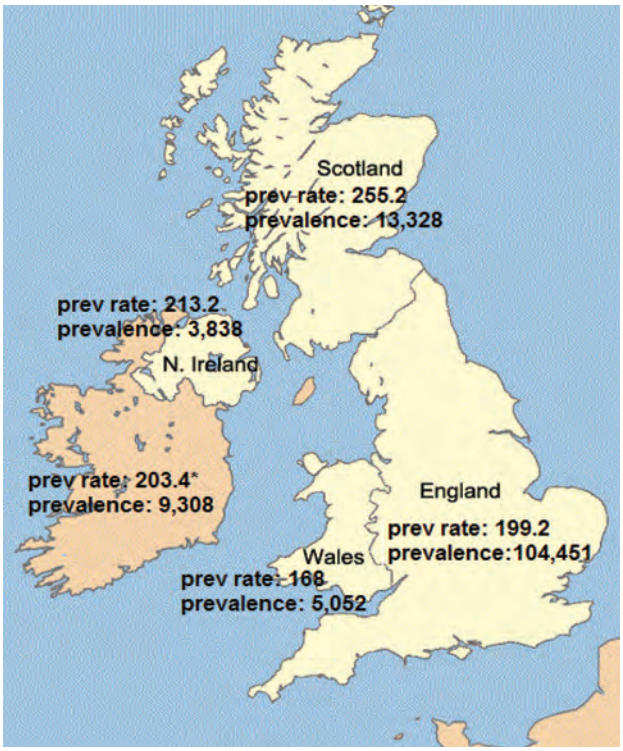


Table 10. Estimated prevalence of MS in Ireland

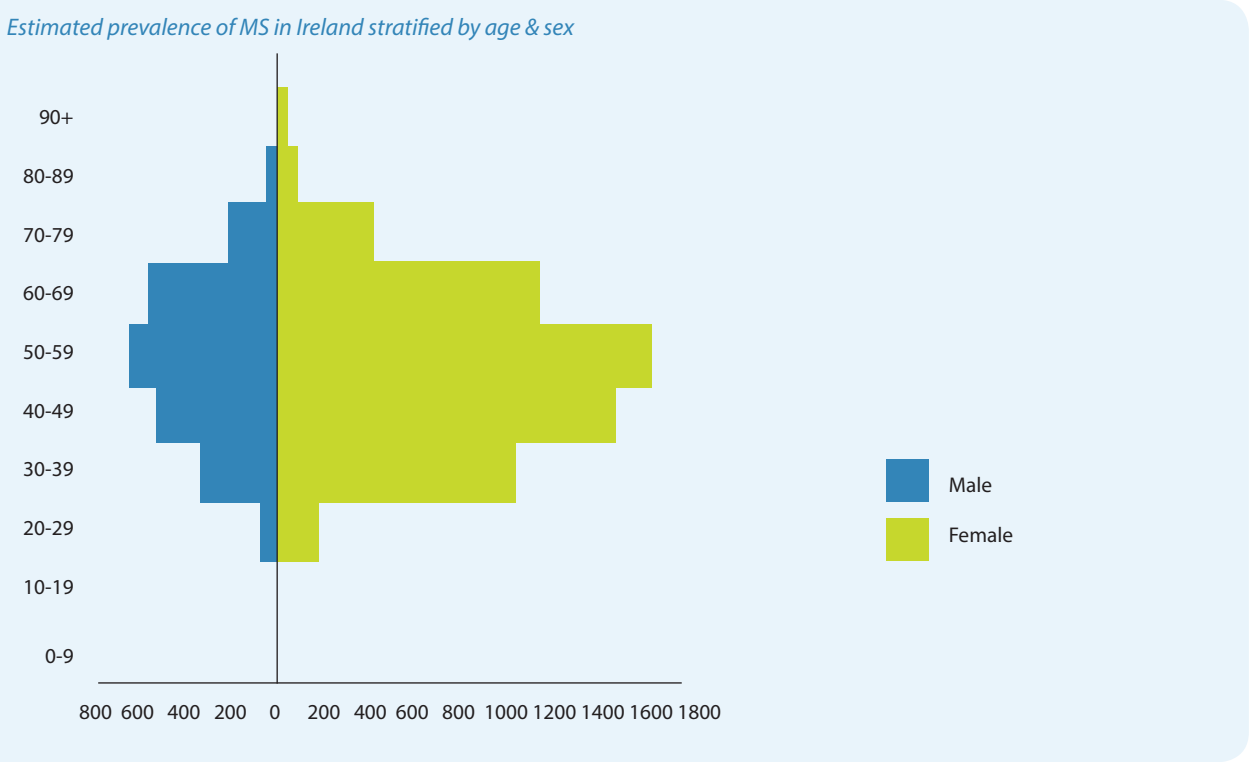
Age group	Irish Population	Prevalence rate in UK ($/10^5$)	Prevalent cases IRE
Male			
0-9	346,113	0.3	1.04
10--19	299,338	2.4	7.18
20-29	320,350	19.6	62.79
30-39	377,011	88.8	334.79
40-49	317,846	166.5	529.21
50-59	258,858	248.8	644.04
60-69	196,167	287	563.00
70-79	110,107	183.9	202.49
80-89	42,014	72.7	30.54
90+	4,895	35.6	1.74
Total Male	**2,272,699**	**114.9**	**2,611.33**
Female			
0-9	330,986	0.2	0.66
10--19	286,172	3	8.59
20-29	338,003	58.4	197.39
30-39	381,195	274	1,044.47
40-49	318,151	470.2	1,495.95
50-59	260,050	638.7	1,660.94
60-69	196,257	597	1,171.65
70-79	123,119	340.8	419.59
80-89	67,986	156.6	106.47
90+	13,634	79.1	10.78
Total Female	**2,315,553**	**289.2**	**6,696.58**
Both sexes all ages	**4,588,252**	**203.4**	**9,307.91**

This analysis also provides an interesting insight into the distribution of MS across ages and across genders. The population pyramids below show that the peak age of MS is most prevalent in the 50-59 age groups for both men and women (see Figure 5 Prevalence – population pyramid)

While serving as a good guide to the prevalence and MS in Ireland, the estimate reported here should however be viewed as being a conservative one. Firstly, the UK study estimated the prevalence of those who had received a diagnosis of MS from their GP; it seems probable that there remains a proportion of the population with MS who remain undiagnosed.

Secondly, while adjusting for age and sex may be expected to capture most of the variation between the populations of the UK and Ireland one may have concerns about the natural congruency of these populations with regard to ethnic heterogeneity. Indeed as of 2011, Ireland's population was 95% Caucasian whereas in the UK this figure was 86%.

Figure 5. Prevalence of MS – population pyramid



5.2.4 Secondary Sources

As aforementioned, there is no national registry of people with MS in Ireland. There are, however, some sources which provide an insight into the number of people with MS in Ireland. First of all, MS Ireland has a list of registered members of people with MS. MS Ireland's personal database has a specific category for those registered members who have MS, and the total number in this category stands at 6,098. We can confidently assume that this figure is an underestimate of the total prevalence of MS in Ireland, as not all people with MS are registered with MS Ireland and MS Ireland currently operates from the approximation that as many as 8,000 people in Ireland live with MS.

A different approach to try quantifying the number of people living with MS in Ireland is to look at the number of medicines prescribed for the treatment of MS and calculate back the number of patients taking specialist MS products. Using average posology and general market information from IMS medicines sales data, and insight from clinical practice, we estimate that approximately 4,401 people with MS are prescribed disease modifying treatments (DMTs). Utilising that figure (4,401) and assuming that 61.4% of those with mild MS and 29.6% of those with moderate MS are taking a DMT (Fogarty et al., 2014), provides us with a total prevalence estimate of 9597 people in Ireland living with MS.

A more precise estimate could be generated, if Ireland had a national registry of people with MS, or if the HSE made publicly available aggregate statistics of persons with MS who hold medical cards or long term illness cards.

5.3 Summary

It is important for cost of illness studies to use accurate and up to date information on the prevalence and incidence of disease to truly understand the impact of the disease on society. While this chapter is not a precise estimation of the prevalence and incidence of disease, the broad overview it provides of the available indicative evidence of the epidemiology of MS allows us to make certain conclusions.

First of all, as the table below shows, it is likely that the total prevalence of MS in Ireland is between eight and ten thousand. Such a conclusion was arrived at by looking at the available databases and applying prevalence rates from Irish, Northern Irish and UK studies, to the Irish population according to the most recent census in 2011. It must be noted, that unlike the UK GPRD study, the results generated from the Northern Ireland have not been age and sex adjusted.

Table 11. Prevalence of MS in Ireland, range of estimates

Source	Prevalence Rate / 10^5	Prevalence of MS in Ireland in 2011
MS Ireland database of members	174.4*	8,000
Inference from IMS Sales data	209.2*	9,597
Most recent Irish prevalence study (Lonergan et al., 2010)	187.5	8,603
Extrapolating from UK GPRD study (Mackenzie et al., 2013)	203.4	9,332
Extrapolating from most recent NI study (Gray et al., 2008)	230.6	10,580

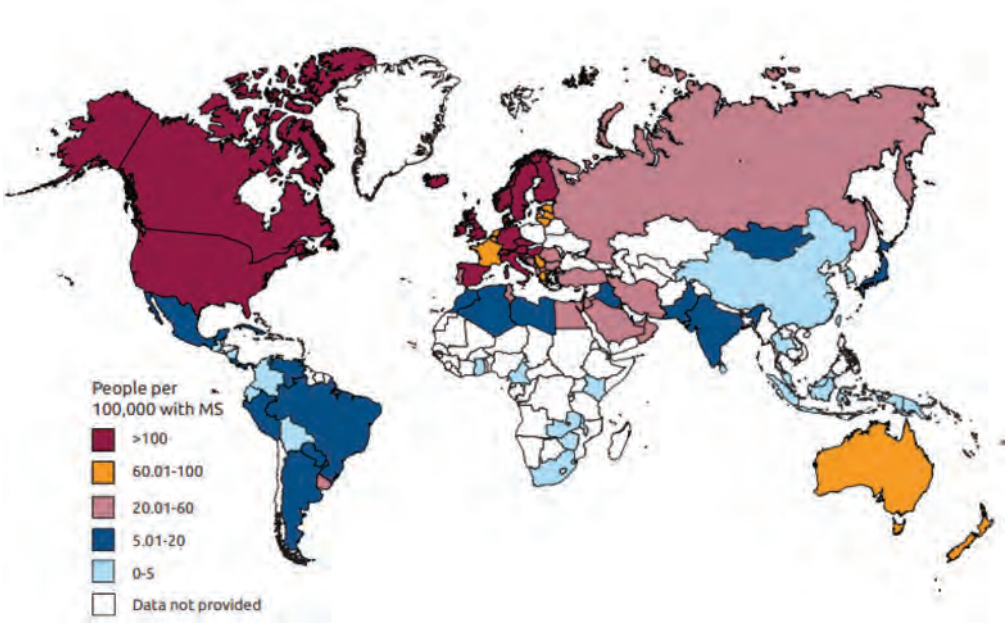
*Prevalence rate estimated as not reported

Further inferences can be made about the prevalence of MS across the sexes, age groups and the breakdown of prevalence according to the four different forms of MS, from the overview of the epidemiology of MS that this chapter provides. As has been stated repeatedly in the medical literature, MS is more common in women, for example according to the GPRD study women accounted for 72% of prevalent cases in Ireland. Also the GPRD study showed that the age of onset of MS peaked at the 30-39 age group in women, and the 40-49 age group in men. Regarding the prevalence of MS across the various disease subgroups, the most recent study from Northern Ireland by Gray et al. (2008) found that the most common form of MS was RRMS (56.6%) followed by SPMS (36%) and PPMS (7.4%).

As the picture below shows from the Atlas of MS study, Ireland has one of the highest prevalence rates in the world. Indeed, the global median prevalence of MS was 33 per 100,000 (in 2013) according to the Atlas of MS study. The high prevalence of MS in Ireland, along with the early onset and long duration of the disease indicates the costs of MS to society is likely to be significant, which in the chapters that follow we will estimate in this report.

Figure 6. MS International Federation: Atlas of MS, 2013

PREVALENCE BY COUNTRY (2013)



My MS Story

"MS doesn't mean my life is over"

On the 3rd of October 2005, I woke up and my arm was asleep, I thought nothing of it and expected that it would pass after a few minutes. This didn't happen and as the morning progressed my leg became limp also. I thought it must be a trapped nerve or something. I felt overwhelmed with tiredness and around lunch time decided to take a nap. I didn't wake up till 7am the following morning only to find my arm and leg were still limp.

I went to see my G.P. who sent me to St. Vincent's University Hospital. After an MRI and a lumbar puncture Professor Niall Tubridy told me that it was possible that I had MS. I felt like I had been hit with a four by four, my head was a mess. I left hospital after a month and although I could walk and use my arm again after physiotherapy, they were still weak. On the 29th of January 2006 after another MRI, I was told that I had MS for sure.

The next few years were a nightmare. I was a teacher and basket ball coach in secondary schools; I also researched, produced and presented an hour long chat programme for Dublin City Radio. After only a year I was no longer working. I became depressed and stayed that way for several years. Eventually I had a complete breakdown and was suicidal.

With a lot of support both medically and from the MS Society I began to see the light and acceptance came. As the stress eased my symptoms lessened. I am on constant strong pain medication, the muscle in my bowel died and I get tired a lot. I've learned to listen to my body and know my limitations and life has become easier.

I'm now studying print journalism at DCFE. At the end of each day I'm exhausted and I've had a lot of infections. However, I'm really enjoying the course and keeping up with the assignments. It took me a few years to understand that having MS doesn't mean my life is over. I just needed to adjust and learn to live 'just for today.'

Therese, Dublin

6. Societal Cost of MS in Ireland: Methodology

6.1 Study Approach

The study is based on the methodology used in several earlier studies of the cost of MS in Europe, the US and Canada. In particular the national cost of MS studies carried out by Kobelt in nine European countries heavily influenced the structure and themes of this survey, to allow for a broader comparison of results (Kobelt et al., 2006b). Insofar as we used a cross-sectional web-based questionnaire, this study used a similar methodology to Karampampa et al. (2012a)

This research can therefore be best categorised as a descriptive 'cost of illness' study using 'bottom up' data collection strategies where costs are estimated in a sample of people with MS and extrapolated to the national level. In this case, people with MS were invited to take part in a voluntary national survey relating to their disease and associated resource use and experiences.

With regard to the estimation of the costs, a prevalence based approach was used which can be understood as the total costs arising from MS within a given year. An alternative approach is an incidence based approach in which the costs of a disease are modelled over the life time of individuals, and these costs then summed up to give to give a national account. This latter approach is considerably more challenging and data intensive. The prevalence approach is used most often and results in a more policy relevant account of the costs of MS (given annual budgetary cycles).

In all cost of illness studies, the perspective taken is fundamental. Costs can be presented from many different viewpoints, the individual, family and society and specific healthcare providers – both private and public. In general the societal perspective is advocated by economists as it provides the most complete view (Kobelt et al., 2006b). In this study, the societal perspective was adopted throughout.

Costs of illness studies, from a societal perspective, are interested in the total costs to all those affected (people with MS, caregivers, family) by a medical condition. The three typical cost categories that are considered are the direct costs (i.e., the medical costs directly related to an illness); the indirect costs (i.e., costs arising to the individual or society as a result of the illness –e.g., ability to work); and lastly intangible costs (i.e., the costs attributable to non-market 'goods'; they are considered intangible as there is no market price but these costs can be measured using 'willingness-to-pay' methodologies amongst others). Important examples in this context include disability, pain and suffering.

In estimating these three costs categories, it is the aim of this research to provide a comprehensive assessment of the societal costs of multiple sclerosis in Ireland

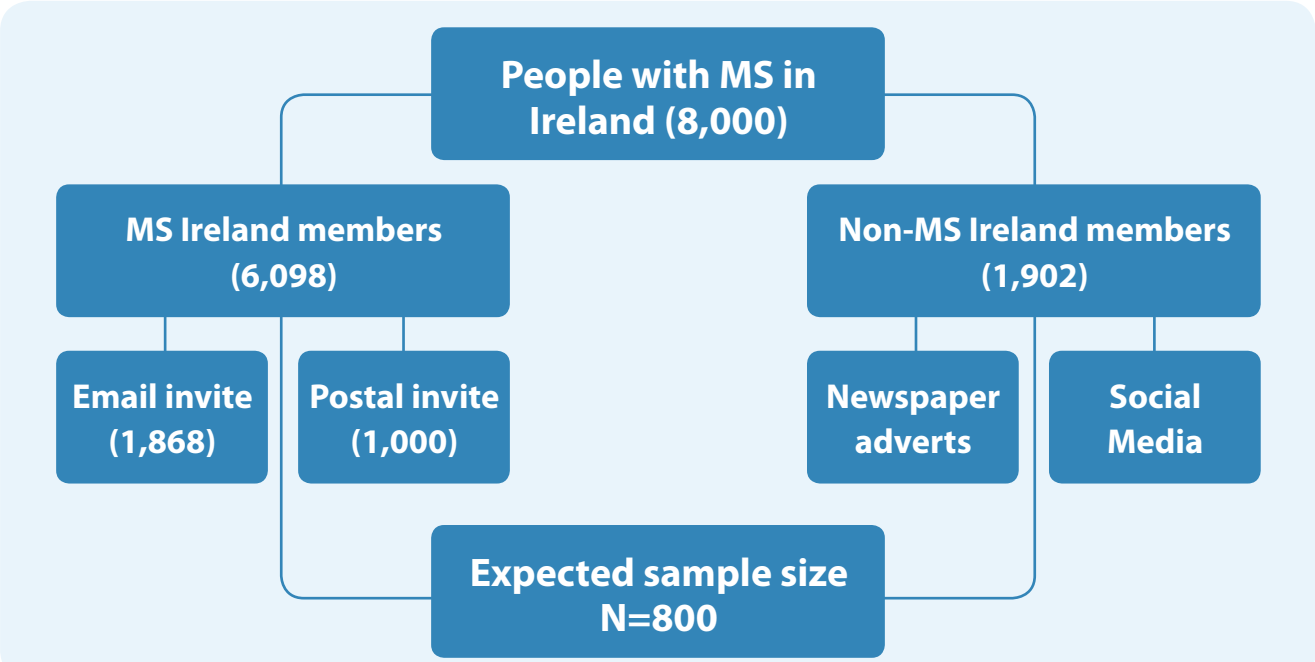
6.2. Participant Recruitment

The aim of this research is to study the cost of MS from a larger and more nationally representative sample of people with MS. Previous Irish studies, as noted earlier, have examined the issue of cost however these estimates are evaluated using a clinic-attending sample at one neurological centre in South Dublin. A question as to how nationally representative this group and the associated costs remains. With this aim in mind, MS Ireland invited all people with MS, living in Ireland, to complete a questionnaire to capture the costs of MS. This cross-sectional, self-reported survey was hosted online for one month in early 2015, and paper questionnaires were made available for those who did not have access to the internet and wished to participate.

MS Ireland invited by email the members of their own organization (N= 6,098) to participate; where no email was available a postal invitation was sent. There was also a concerted effort to recruit people with MS who may not be members of MS Ireland to ensure that the sample was broadly representative of the MS population in Ireland. The recruitment of non-MS Ireland members was sought through notification of the survey in the national press, and through non-traditional media channels (i.e., blogs, Twitter, Facebook). The complete recruitment strategy is detailed in Figure 1 below.

Respondents were included once they confirmed to have a clinical diagnosis of MS or clinically isolated syndrome (CIS) and were over the age of 18 and gave their informed consent to participate. A total of 825 participants entered the survey. Of these, 198 respondents did not complete or submit their answers at the end of the survey, another 22 reported not having a diagnosis of multiple sclerosis (or clinically isolated syndrome), eight respondents did not give indicate their consent; one person indicated not being 18 or older. In addition to this, two respondents gave consistently implausible responses and were also excluded. In total, 594 people were included in the final sample, 20 of those were postal responses. The EuroQol EQ-5D-5L component was completed by 542 respondents.

Figure 7. Recruitment strategy



6.3 Survey Design

The international cost of MS literature was reviewed to inform the design of the questionnaire along with input from local neurologists and health economists. The structure of the survey can be divided into six sections: disease information, resource utilisation, relapses, productivity, care needs, and HR-QoL. These sections are each discussed in more detail below.

6.4 Disability Severity

Unlike a clinic-based study, our survey relies on people with MS recalling and self-reporting on their condition. This self-reporting approach is often less preferred by clinicians who rely on often subtle disease signals and clinical acumen to manage MS. The alternative argument, from an advocacy perspective, is that the person with MS—through living with their condition—are *de facto* experts on the experience of living with MS and the impact it has on their lives and the lives of their families. So while validated survey instruments—more commonly found in clinic-based studies—are included for comparability and classification purposes, the personal insight and experience is given primacy in this study.

One of the most common clinical instruments in the MS literature is the Expanded Disability Status Scale (EDSS). This is the main method of quantifying disability in MS and monitoring changes in the level of disability over time. The EDSS scale ranges from 0 to 10 in 0.5 unit increments that correspond to increasing levels of disability. Given the potential for 20 different levels of disability with the EDSS, a neurologist completes the scoring. In our study, in order to broadly stratify people with MS according to their EDSS score three classes of disability were consider mild, moderate and severe MS. It can be considered, under an a simplified means of approximating EDSS, 'mild' approximates an EDSS of 0-3, 'moderate' from 3.5 to 7, and 'severe' from 7.5 to 10. Three statements (or symptom vignettes) were constructed based on the EDSS classification system and prior literature to reflect the three classes of disablement – mild, moderate, and severe. This question was reviewed and approved by two neurologists. This question is provided below.

Figure 8. Questionnaire – MS Severity

The statement below shows three levels of disablement (mild; moderate; severe). Please tick the category which most closely reflects your general level of disability these days.		
Mild	**Moderate**	**Severe**
I am independently mobile with minimal disability	I have a moderate level of disability. My mobility is somewhat restricted and sometimes I depend on others to perform day-to-day activities.	I require a high level of assistance for all activities of daily living

Respondents were also asked to report their form of MS; RRMS, PPMS, SPMS, benign disease, Clinically Isolated Syndrome or whether they did not know. For respondents with the most common form of MS (i.e., RRMS) the frequency and severity of relapses were important to capture with some consistency. To achieve this, respondents were provided with the following definition of a relapse, before being asked to record their own experience with such events.

Figure 9. Questionnaire – Relapse Definition

"The appearance of new symptoms related to your MS or very definite worsening of old symptoms, which lasted for at least 24 hours and occurred after you had been stable for at least a month and when you did not have a temperature, an infection or any other health trouble"

Respondents also reported whether the relapse they recall and report was also confirmed by a member of a neurology team. Like MS in general, relapses can also be classified as mild, moderate or severe. O'Brien et al. (2003) classifies relapse as low, moderate and high intensity according to the level of health services required to manage the relapse[13]. The Irish study on the cost of relapses by O'Connell et al. (2014) stratifies relapses according to this typology also. Our study adopts two separate approaches to assessing relapse severity or intensity. We use the O'Brien et al. (2003) approach by asking participants to report what healthcare services they required to manage their last relapse (i.e., what healthcare services they used) and also a more subjective assessment of self-assessed 'impact on daily life'. This latter measure is expected to capture those who had-recalled relapses that had a substantial impact on daily living and thereby an indirect cost rather than only the clinically confirmed relapses that required (by definition) contact with healthcare services. While neither measure can be considered satisfactory in isolation, we consider it important to include both measurements to account for more and less subjective assessments of relapse. The question regarding impact of relapse on daily life as shown below.

13. A low intensity episode was defined as evidence of minimal disability on examination requiring only symptomatic management or a short course of oral steroids. Moderate intensity episodes were treated with intravenous steroids in the outpatient setting either as a day case in the infusion therapy unit in the hospital or if available at home and high intensity episodes required hospital admission

Figure 10. Questionnaire – Impact of Relapses on Daily Life

'Another way of measuring relapse activity is, rather than just your need for medical intervention, is the impact of relapses on daily life. Thinking back to the relapses you experienced in the past year, how many of these relapses had...'

	Number
No impact on your life: You had some familiar symptoms that passed quickly without any impact on your regular activities. (1)	☐
Mild impact on daily life: You had symptoms that did impact your life, without much disruption. (2)	☐
Moderate impact on daily life: You had symptoms that limited your ability to work (e.g. took less than two days off work), and / or limited your social activity. (3)	☐
Severe impact on daily life: You had symptoms that significantly limited your productivity, mobility and independence (e.g. Took 3 or more days off work, had to rely on others) (4)	☐

6.5 Resource Assessment

6.5.1 Direct Healthcare Resources

The survey was designed to capture frequency information to inform a calculation of the direct costs associated with MS in general and to those specific to MS relapses. Information on resource utilisation was collected through questions based on the Client Service Receipt Inventory (CSRI), and adapted to the setting of the study. The CSRI is a research instrument applied for the collection of information on costs and has been widely used in cost of MS studies (Fogarty et al., 2014, McCrone, 2009). The length of the recall period varied depending on the expected frequency of resource use, e.g., for inpatient admissions a recall period of 12 months (i.e., 1 year) was given while for 'investigations and diagnostic tests' and GP visits a six month period of recall was given; for home help a 1 week recall period was used. For non-routine items such as 'mobility and other living aids' (e.g. crutch, wheelchair, utensils) and 'home modifications' the full duration of the disease was used for recall.

For expediency and to reduce the burden on the survey respondents, detailed information regarding current medication use was not requested– as the societal cost of these can be imputed using alternative sources.

6.5.2 Indirect Resources

Alongside our effort to measure the direct costs of MS, we were particularly interested in estimating the less salient indirect costs of MS. The nature of these costs, as suggested by their name, makes them more difficult to estimate. Some of the more substantial items like productivity losses and informal care were given more attention given that MS is generally diagnosed among otherwise healthy young adults. With regards to productivity losses, questions were asked to measure the extent of labour force participation, unemployment, permanent withdrawal from the workforce, reduced working hours and sick leave related to MS. We adapted the questions from a validated survey instrument, the 'Work Productivity and Activity Impairment – General Health' questionnaire to assist in estimating the indirect costs resulting from reduced productivity (Reilly et al., 1993). These latter productivity-related questions asked participants to reflect upon the past seven days and state how much time was missed from work, how their work performance was affected, and whether MS affected ones abilities to partake in regular daily activities outside of work.

i. Productivity losses

Productivity losses were measured in this study using the human capital (HC) approach. The HC approach treats people as assets and values life and health as the changes in production to the economy (Zhang and Anis, 2014). It assumes that the value to society of productivity loss should be measured as the present value of lost time according to the market wage, which in economic theory is supposed to equal the marginal revenue product (MRP) of labour in a competitive labour market (Krol and Brouwer, 2014). Following this approach, productivity losses associated with reductions in working hours or sick leave and permanent withdrawal from the work force, due to MS, were based on national gender-stratified average gross hourly and annual earnings, respectively.

ii. Presenteeism

Presenteeism relates to lost productivity at work due to health problems. Presenteeism arises when a person attends for work but is not performing their duties as expected in terms of quality or quantity. The situation may arise when suffering ill-health. The costs associated with presenteeism can be substantial and in may even outweigh those related to absenteeism (Krol and Brouwer, 2014).

In the present study, the respondents were asked the following question: 'During the past seven days, how much did MS, on average, affect your work performance?' Here a response of zero indicated that work performance was not affected at all by the symptoms of MS, a score of five indicated that that work performance was reduced by half, while a score of ten indicated that the respondent was completely unable to perform their work duties. The cost of presenteeism associated with MS was calculated by annualising the work performance affected, equating same to work-time missed and presenting the lost productivity in terms of mean gender-stratified annual earnings.

iii. Informal care

Informal care is another indirect cost that was estimated in this study. The costs of informal care was estimated based on the hours of care provided and whether the caregiver had officially reduced their working week or given up their own job in order to provide care.

Questions were also asked about whether the caregivers ever had to take extra unscheduled days off work to provide care duties. Thus, these questions provided a clear picture regarding the productivity losses of the caregiver, which is an often unnoticed cost in cost of illness studies.

As an extension of the Human Capital approach, informal care was valued using the opportunity cost method, as earnings foregone as a result of time spent caregiving. Here we include earnings foregone up to a maximum of 40 hours per week and value same using the national gross mean hourly wage in Ireland (CSO, 2014). Although it is the case that for many carers, the amount of care provided will be in excess of 40 hours, applying this cut-off point ensures a more conservative estimate. This approach mirrors that used in a recent Irish study (Fogarty et al., 2014)

iv. Depression & Anxiety

It was expected that the levels of depression and anxiety in our sample population would be considerably higher than in the general population, as is clearly demonstrated in the Irish and in the international literature (Arnett and Randolph, 2006, Beiske et al., 2008, Kronfol, 1985, Brown et al., 2009, McGuigan and Hutchinson, 2006). As a case in point, McGuigan & Hutchinson. (2006), found that 28% of their sample of Irish people with MS (n=211), displayed moderate to severe depressive symptomology. A rate which is 3.5 times higher than has been reported for the general population (Ayuso-Mateos et al., 2001)

Comorbid depression and anxiety is likely to serve to further increase direct medical costs associated with MS, via increased healthcare utilisation and medication use. We estimated the prevalence of diagnosed depression in our sample by asking the following question: '*Since the onset of MS, has a doctor ever diagnosed you with, or treated you for, depression*?' A similar question was asked with respect to an anxiety diagnosis. The prevalence rates in our sample could then be subsequently compared with the estimated prevalence rate of mental health problems for the Irish population. In Doherty et al. (2007) a total of 10% of the sample reported speaking at least once to their GP about being anxious or depressed, or about mental, nervous or emotional problems in the previous year, with an average of approximately 4 visits per person. The direct cost of depression and anxiety attributable to MS was then calculated on the assumption that 65% of people that reported having a diagnosis of depression and/or anxiety since the onset of MS in our sample, were being treated for same in the previous year (Arnett and Randolph, 2006). We included the estimate of four extra GP visits per year from Doherty et al. (2007) if the respondent had both an anxiety and depression diagnosis and if depression or anxiety were the sole diagnosis, we assume 3.3 visits and 0.7 extra visits, respectively. Where 3.3 visits is the difference between the annual mean GP visits for the depressed and non-depressed population over 50 in Ireland (O'Regan et al., 2011). We allocate the remaining 0.7 visits to those with anxiety only. We attained annual medication costs of €202.25 and €8.43 from IMS Health data, to provide estimates for treatment costs for depression and anxiety respectively.

6.6 Health Related Quality of Life

Multiple sclerosis, like many progressive diseases, is not just associated with a financial cost but also with a significant emotional dimension that resides outside of the market-based economy.

In economic terms, such a dimension is commonly referred to as 'intangible costs'. Intangible costs generally refer to the costs of pain and suffering, and these are usually apparent in assessments of quality of life (QoL). As the term suggests, intangible costs are difficult to quantify and despite having no financial or transactional value are very much considered real costs. A simple way to appreciate the concept is by acknowledging that people have a willingness-to-pay to avert or avoid pain and suffering. The absence of a market to trade does not in itself make something more or less costly though, without a market *price*, it does give it a less *tangible* cost.

This study applied the commonly used validated survey instrument EQ5D-5L to estimate utility, or health related QoL of people living with MS. This instrument measures QoL over five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The most recent version of this EQ-5D instrument, the five level (i.e., 5L), was used. Permission was granted to use the web and paper version of this instrument by EuroQoL.

Fatigue is the most common symptom or co-morbidity associated with MS. Given its particular significance and its absence, in specific terms, from the EQ-5D, our questionnaire used the short five-item version of the Modified Fatigue Impact Scale (Fisk et al, 1994b). This validated instrument is one component of the MS-QLI: the Multiple Sclerosis Quality of Life Index and has been applied in many MS studies. This instrument provides an assessment of the effect of fatigue in terms of physical, cognitive, and psychosocial functioning (Nat MS-Society). Another Validated survey instrument that was used was the MOS Pain Effects Scale, another component of the MS-QLI. The PES focuses on the ways in which pain and disturbing sensations affect everyday life, an issue for more than 50% of those with MS (Archibald et al., 1994). The complete MS-QLI survey was too burdensome to include in full.

6.7 The annual cost of MS relapse

Supplementary to our calculation of the costs associated with MS in general, the specific costs associated with MS relapses are also of interest given the nature of MS and how it is experienced—especially by those with RRMS; the most common form of MS.

Respondents to the survey were asked to consider their *last* relapse and to answer questions framed under the following headings:

1. Medical Costs of Relapses.
2. Care Needs During a Relapse.
3. Impact of Relapse on Productivity.

This approach, which is consistent with the direction taken to calculate the costs associated with MS in general, allowed us to estimate the direct and indirect costs associated with a single MS relapse. Once the cost of a single relapse is calculated, the resulting estimate will be multiplied by the average number of relapses reported by those who experienced a relapse in the past year (1.85). Thus providing an annual estimate for the cost of relapses in Ireland.

6.8 Unit costs

Irish specific unit costs were applied to each resource component. The sources of unit costs are presented in Table 14. Where applicable, costs were adjusted to the year 2014, using the Consumer Price Index for health (Central Statistics Office www.cso.ie).

6.8.1 Medication costs

For expediency and to reduce the burden on the survey respondents, detailed information regarding current medication use was not requested as part of this study– as the societal cost of these can be imputed using alternative sources. To that end, average medication costs were attained from previous Irish research in the cost of MS area: namely, Fogarty et al. (2014) and adjusted to reflect the levels disability severity in our sample. The average annual medication costs in our study were therefore calculating as being €6,759, per person with MS.

6.8.2 Aids and adaptations

In the absence of standardised unit costs, the cost of mobility/living aids and adaptations were based on those reported in Smith et al. (2011). Home adaptations were calculated on the basis that those reporting such, had adaptations on their home to the value of the average payment received for the Housing Adaptation Grant for People with a Disability, in 2014 (€7,930), plus 5% – as the grant covers 95% of the cost, the full average cost therefore was estimated at €8,347. Following the approach in Fogarty et al. (2014), these costs were annualised assuming a life-span of 5 years (mobility/living aids) or 10 years (home modifications), using a discount rate of 4.0% per annum.

6.8.3 Valuing productivity losses and informal care

Productivity losses were valued following the human capital (HC) approach, where the production forgone due to illness-related absence is valued at the market price for labour (Zhang and Anis, 2014). In this study, the market price for labour is assumed to analagous to average earnings, both hourly €22.04 and annual €35,768, as reported by the CSO for Ireland in 2014. However, as our study sample was 71.4% female and indeed as the MS population in general, is predominantly female – an adjustment was required to stratify annual earnings with respect to gender. This adjustment was made using information from the CSO for the year 2011, as this is the most up to date information concerning the gender pay gap in Ireland.

Of those in paid employment in Ireland, 45% are women, and according to the CSO the average income for these women was 73.5% of men's income, in 2011. Applying these figures to our average annual earnings of €35,768, we therefore estimate national gender-stratified average annual earnings as being €29,848 for women and €40,611 for men.

When adjusted to take account of the average hours per week spent in paid employment, women's average hourly income was about 94.1 % of men's in 2011. Applying these figures to the average hourly wage of €22.04, provides an estimate for national gender-stratified average hourly earnings of €21.30 for women and €22.68 for men.

Productivity losses associated with short-term sick leave and offically reduced working hours were based on national gender-stratified average hourly earnings, while illness-related, permanent withdrawal from the workforce was valued using gender-stratified average annual earnings.

As an extension of the Human Capital approach, informal care was valued using the opportunity cost method, as earnings foregone as a result of time spent caregiving (up to a maximum of 40 h per week), using the national gross mean hourly wage in Ireland (€22.04) (CSO, 2014).

6.8.4 Valuing intangible costs

Intangible costs, i.e., costs due to pain and suffering are difficult to value and consequently are usually omitted from cost of illness studies. However, in Henriksson et al. (2001), the authors provide an interesting approach in estimating these costs in a sample population of people with MS. This methodology for valuing intangible costs has subsequently been used in a number of MS cost of illness studies (Kobelt et al., 2006c, Kobelt et al., 2006b, Casado et al., 2007, Wundes et al., 2010) and for studies in other disease areas (Gannon et al., 2008, Borgström et al., 2006).

We approach valuing intangible costs by calculating the difference in utilities between our sample and an age- and sex-matched sample from a general population (Kind et al., 1999). This method generates an estimate of the number of quality-adjusted life-years (QALYs) lost by the MS sample in one year.

By assigning a value to (or a willingness to pay for) a QALY, intangible costs due to MS can calculated. Although there is no market price or consensus value for a QALY, we construct our estimate assuming a WTP in the range of €20,000 to €45,000 in Ireland. These figures were chosen as they correspond to the thresholds of cost-effectiveness acceptability which are used to determine wither new health technologies are funded in Ireland. of new Interventions which fall in the range of €20,000-€45,000/QALY are conventionally considered cost-effective in Ireland (HIQA, 2014).

Table 12. Source of unit costs

Type of resource	Source of unit cost
Hospital inpatient[1]	HSE-casemix (inpatient DRG)
Nursing home/rehabilitation/respite 2	NHSS / Connolly et al. (2014)
Hospital outpatient consultation	HSE-casemix (average cost per case for an OPD attendance)
Lab/rad/investigations	Tilson et al. (2012) / Bourke et al. (2014)
Investigations and outpatient procedures	HSE-casemix (daycase DRG)
GP	Laya Healthcare Survey
Healthcare professionals, e.g. OT, nurse, etc	HSE salary scales
Medication	Fogarty et al. (2014)
OTC medication	Fogarty et al. (2014)
Aids, e.g. wheelchair, crutch etc.	Smith et al. (2011)
Home modifications	Housing Adaptation Grant for People with a Disability
Formal care (home-help)	HSE salary scales
Private paid help at home	Private company pricelist
Productivity losses	CSO, gross gender specific mean earnings, 2014
Informal care	CSO, mean hourly wage, 2014
Intangible costs	Henriksson et al. (2001)

Table adapted from Fogarty et al. (2014)
DRG diagnosis-related group, GP general practitioner, HSE Health Service Executive, lab/rad/investigations laboratory, radiological and other investigations, MS multiple sclerosis, OPD outpatient department, OTC over-the-counter, CSO Central Statistics Office

[1] Weighted average of HIPE b68(a) & b(68)b, cost per-diem applied on the basis of reported length of stay.

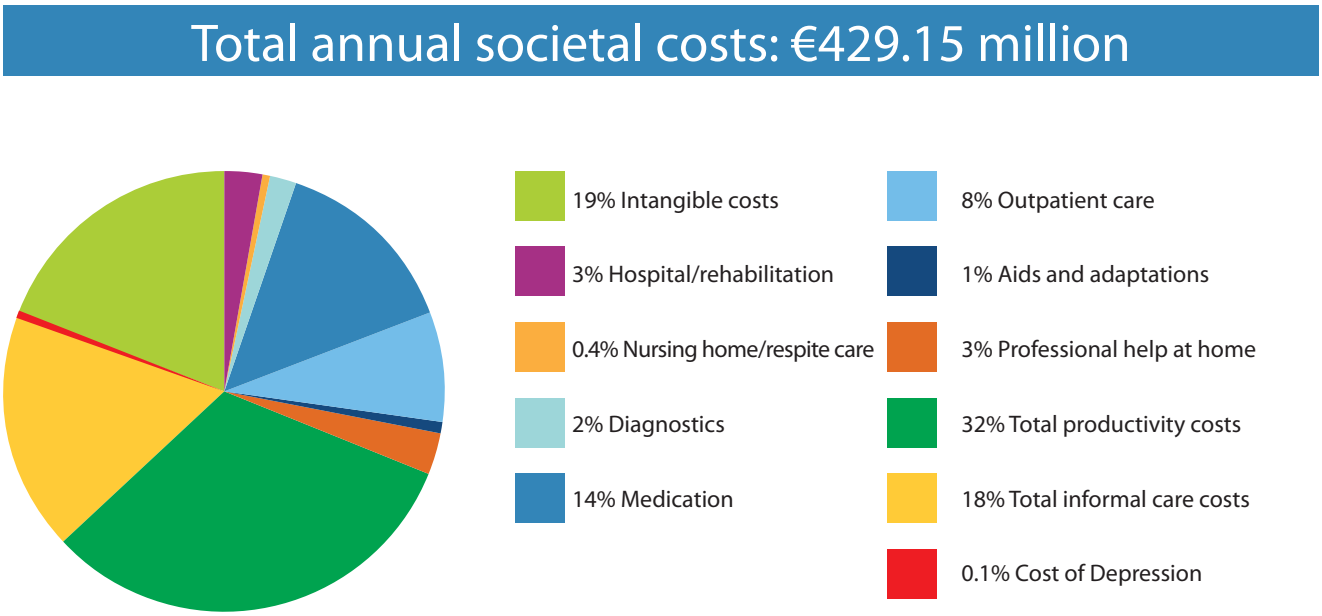
[2] Cost per person in long-stay care is based on the maximum weekly financial support available from the HSE under the Nursing Home Support Scheme (NHSS). The costs used reflects both private and public institutions.

6.9 Analysis

Descriptive statistics were used to analyse the demographic and clinical characteristics of the sample and for the resource utilisation. Percentages, means and standard deviations were reported as applicable. Differences in the demographics and resource use between groups, stratified by disability severity or disease type (i.e., RRMS, SPMS or PPMS) were compared by ANOVA and Wilcoxon–Mann–Whitney test, for parametric and non-parametric data, respectively. Statistical significance is based at the 0.05 level throughout. Stata 13 was used for all statistical analysis.

7. Results

Figure 11. Total annual costs by resource use: Direct, indirect and intangible costs



7.1 Descriptive statistics

As expected, and consistent with the epidemiological literature (Pugliatti et al., 2002, Rosati, 2001), the majority of our sample were female, at around 71%. The mean age was 47 years and 78% of our sample were between the ages of 30-59 years. The bulk of our sample were married or cohabiting (65%), while some 20% reported living alone. 38% reported having no children while 15% and 47% responded that they had one child or more than one child respectively. The breakdown of our sample with respect to province of residence is consistent to that of the general population of the Republic of Ireland, therefore we assume our sample is broadly representative of the national population of people with MS (see Figure 26, in Appendix)

Table 13. Background information (n=594)

Age characteristics	
Mean (SE) (years)	47.03 (SE 12.16)
Proportion ≥65 years	8.1
18–29 years	6.57
30–39 years	23.95
40–49 years	26.47
50–59 years	27.82
60–69 years	11.97
70–79 years	2.7
≥80 years	0.51
Sex	
Female n (%)	424 (71.38)
Male n (%)	170 (28.62)
Marital status n (%)	
Single	156 (26.31)
Married/Cohabiting,	388 (65.32)
Widowed	11 (1.85)
Separated/Divorced	38 (6.41)
Habitation, n (%)	
Live alone	116 (19.83)
Live with others	464 (79.32)
Live in a care home	5 (0.85)
Children, n (%)	
0	224 (37.77)
1	95 (15.97)
> 1	276 (46.26)
Breakdown of sample by province %	
Leinster	59.2
Munster	24.3
Connacht	10.3
Ulster	5.4

7.1.1 Disease information

The average age of disease onset was just over 32 years of age. The mean duration of disease –that is the period of time since first developing MS symptoms—was nearly 15 years.

The mean age in our overall sample was 47 years. As expected, the mean age varied by disability severity and disease type. The average age of those with severe disability (55 years) was higher than those with moderate (51 years) and mild MS (55 years). A similar pattern was observed with respect to disease type: the average age of those with RRMS was 44 years, while those with SPMS and PPMS, on average were 54 and 56 years old, respectively.

The majority of our respondents (63%) reported having the relapsing remitting form of the disease, 16% reported having secondary progressive MS (SPMS) and 11% had primary progressive disease; over 6% reported not knowing their current course of disease.

Most of the people in our study reported having mild MS (57.6%), 35.6% reported having moderate MS, while some 7% reported having severe disability.

There was varying levels of disability severity within each disease type: 73.7% of those with RRMS reported having mild MS, while 26.6% and 0.7% reported moderate and severe disability, respectively. The majority of those with SPMS reported having moderate disability (67%) and 22% and 11% reported either severe or mild disability. A similar pattern emerged with respect to those with PPMS, once more the majority reported being in the moderate category (62.2%), while 19.6% and 18.2% disclosed having mild and severe disability, respectively.

Almost 42% reported having had a relapse in the past year with an average of 1.8 reported relapses per respondent; 53% reported that the relapse they had experienced last year had been confirmed by a neurologist. Unexpectedly, relapses were reported across all levels of disability and disease types: 38% of those with mild MS reported having on average 1.6 relapses in the past year, while 49% and 34% of those with moderate and severe MS reported 1.9 and 3.1 relapses, respectively. So too when it came to disease type: 46% of those with RRMS reported 1.7 relapses in the past year, while it was the case that 44% and 21% of those with SPMS and PPMS reported 2.2 and 2.1 relapses, respectively. It must be noted however, that although the study respondents were provided with a global definition of a MS relapse[14]–a person's definition of a relapse may not be the same as a medical definition. Indeed, just over half of those experiencing relapses, reported having them confirmed by a neurology team. Being that as it may, our survey relies on people with MS recalling and self-reporting on their condition, therefore the personal insight and experience offered by the respondents, is given primacy in this report.

The respondents in our sample also reported having been diagnosed or treated for psychological comorbidities since the onset of MS, 33% with depression and 26% with anxiety. More than 90% of our sample reported fatigue as a consequence of their condition. There was a degree of heterogeneity when it came to depression and anxiety in our sample with respect to levels of disability severity and disease type (we deal with this separately in this report, see 7.4.3.

Table 14. Disease information

Disease information	N (%)
Age at MS onset, mean (years) (SE)	32.3 (10.0)
Duration of disease, mean (years) (SE)	14.7 (10.7)
Course of disease, n (%)	
Relapsing remitting	374 (62.9)
Secondary progressive	97 (16.3)

14. "The appearance of new symptoms related to your MS or very definite worsening of old symptoms, which lasted for at least 24 hours and occurred after you had been stable for at least a month and when you did not have a temperature, an infection or any other health trouble"

Primary progressive	66 (11.1)
Benign	13 (2.2)
Clinically Isolated Syndrome	7 (1.2)
I do not know	37 (6.2)
Disability severity, n (%) (self-reported)	
Mild	342 (57.6)
Moderate	211 (35.6)
Severe	41 (6.9)
Relapses	
Relapse in previous 12 months, n (%)	247 (41.6)
Average number of relapses (n) (SE)	1.8 (1.1)
Confirmed by a Neurologist	131 (53.0)
Disease impact	
Depression diagnosis since onset of MS, n (%)	195 (32.8)
Anxiety diagnosis since onset of MS, n (%)	156 (26.3)
Experience fatigue due to MS, n (%)	549 (92.4)

7.1.2 Employment characteristics

A sizable proportion of our sample reported that they were in paid employment (42.8%) and, *of those working, 74%* were doing so in a full-time capacity. The average working week for a full-time employee was just over 39.6 hours, while those in part-time employment, worked 19 hours per week, on average.

Over 27% of our sample reported having to permanently withdraw from the workforce *due* to their condition.

In terms of disruption, *of those working* 33.5% had officially reduced their working hours, while 26% and 70%, had felt it necessary to change career path and felt that MS had limited their career potential, respectively.

In total 40.6% of our sample were in receipt of some form of state benefit. However, in this study, we have not included any money that people with MS receive from the state in the form of disability/illness/invalidity payments, as from an economic point of view these payments are simply transfers that do not impose any cost on society

Table 15. Employment characteristics

Employment status, n (%)	**n (%)**
Employed	(254) 42.8
Full time (over 30hrs per week)	(188) 74.0
Average Hours per week	(254) 34.2hrs
Situation of those who are not employed, n (%)	
Housewife/husband	(55) 9.2
Student	(25) 4.2
Retired due to age	(29) 4.9

Retired early due to MS	(162) 27.3
Unemployed but seeking work	(24) 4.1
Leave of absence	(14) 2.4
Unable to work but intend to return	(41) 6.9
Employment experiences of those working (n=254)	
Reduced their working hours	(85) 33.5
Had to change career	(66) 26.1
Felt that MS limited their career potential	(174) 68.5
In receipt of state benefit	
Disability Allowance	(79) 13.3
Illness benefit	(32) 5.4
Invalidity Pension	(130) 21.9
I do not receive any of the above	(353) 59.4

7.1.3 Quality of life

7.1.4 EQ-5D and QALYs lost

The EQ-5D-5L is a self-reported generic HRQoL instrument that was developed by the EuroQol Group (Herdman et al., 2011, Group, 1990). Respondents report their level of problems experienced in five domains of health: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression, indicating whether they are having no problems or slight, moderate, severe or extreme problems in each assessed domain. Based on the combination of responses, respondents are classified into one of 3,125 unique EQ-5D-5L health-state profiles.

To rank value, each health state can be converted to a single utility value representing general population preferences (Oppe et al., 2007). Utility is measured on a cardinal scale anchored at 1 (perfect health) and 0 (absence of life/dead). Valuations less than zero (as low as -0.594), reflecting health states 'worse than death' (WTD) can exist.

In the EQ-5D instrument, respondents are also asked to report their self-rated health via the EQ-VAS; a tool, which using a 20-centimeter vertical visual analogue scale, with endpoints ranging from 0 to 100, asks the individual to label their health between zero "*the worst health you can imagine*" to one "*the best health you can imagine*" (Oppe et al., 2007).

In our sample, the EQ-5D-5L was completed by 541 people. In order to map the EQ-5D-5L to the EQ-5D-3L value set for the UK,the mean utility for the sample was derived by using the "EQ-5D-5L Crosswalk Index Value Calculator",. This methodology also allowed us to calculate crosswalk index values for the EQ-5D-5L dimension scores (van Hout et al., 2012). This method is the most commonly accepted while local preference elicitation studies based on the EQ-5D-5L are ongoing in Ireland (Fogarty et al., 2013).

The mean utility for the sample derived by using this approach was 0.587. when compared to the UK population norm of 0.86, this represents almost a 32% decrease in self-reported QoL (Kind et al., 1999).

There was also a significant difference between the men and women in our sample with scores of 0.507 and 0.619 respectively ($P < .01$).

There was a graded relationship between self-reported severity of disability and utility value, those with mild, moderate and severe disability reporting mean values of 0.718, 0.492 and -0.027 respectively. Negative values are possible with the EQ-5D as some people may judge health states as being worse than death, this is the case for those reporting severe disability in our sample.

Differences were also apparent with respect to disease course, those with the RR form of the disease reporting significantly higher mean index values (0.67) than SPMS (0.34) and PPMS (0.39) ($p<0.001$). Those with the primary progressive form of the disease reported higher utility values on average, than those with SPMS – however, this difference was not statistically significant ($p=0.38$).

There was also a difference in the mean utility score between those who did and those who did not have a relapse in the previous year, although this difference did not reach statistical significance ($p=0.189$). However, when we restrict our sample to just those with RRMS, a significant difference existed, with those experiencing a relapse reporting lower utility values (0.64), than those in the no relapse cohort (0.70) ($p<.02$). The mean Visual Analogue Scale (VAS) score for our sample was 63.34.

Table 16. EQ-5D sample characteristics (mean utilities)

EQ-5D-5L	N (%)	Mean (SE)
Entire sample		
Mean EQ-5D-5L index value	541 (100)	0.59 (0.29)
Sex		
Women	386 (71.3)	0.62 (0.26)
Men	155 (28.7)	0.507 (0.33)
By MS severity		
Mild	312 (57.7)	0.718 (0.19)
Moderate	192 (35.5)	0.492 (0.22)
Severe	37 (6.8)	-0.027 (.26)
Disease course		
RRMS	346 (63.4)	0.67 (0.20)
SPMS	90 (16.6)	0.34 (0.33)
PPMS	55 (10.2)	0.39 (0.34)
Relapse in past year		
No	307 (56.7)	0.60 (0.30)
Yes	234 (42.3)	0.57 (0.28)
Visual analogue scale (entire sample)		
VAS	541 (100)	63.34 (21.7)

For those in our sample, issues relating to mobility were deemed most problematic, with 46.2% reporting having at least moderate problems with walking about. This was followed by usual activities, e.g. work, leisure activities (43.4%), then pain or discomfort (42.5%), followed by anxiety or depression (24%) and finally self-care, e.g. washing, dressing (18.7%).

Table 17. EQ-5D-5L Domains

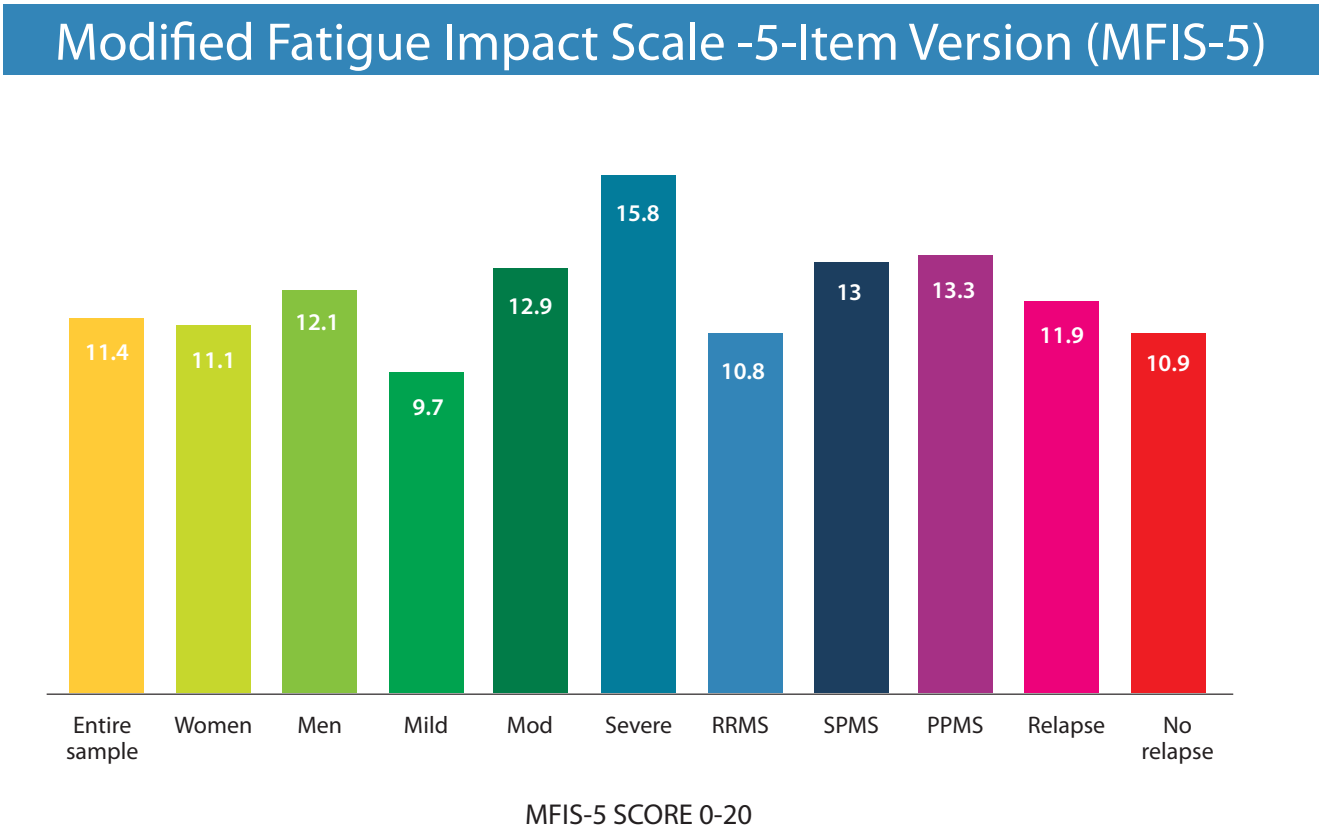
Level of problems	Mobility	Self-care	Usual activities	Pain or discomfort	Anxiety or depression
No problems	27.7%	60.6%	22.7%	21.8%	40.5%
Slight problems	26.1%	20.7%	33.8%	35.7%	35.5%
Moderate problems	26.1%	10.5%	28.1%	29.9%	20.3%
Severe problems	12.0%	4.4%	11.3%	10.0%	2.8%
Extreme problems	8.1%	3.7%	4.1%	2.6%	0.9%

i. Fatigue

The impact fatigue has on the daily lives of the people in the sample was measured by implementing the Modified Fatigue Impact Scale (MFIS), the five-item version in our survey (Guidelines, 1998). The items ask whether, because of fatigue during the past 4 weeks: *Have you been less alert? Have you been limited in your ability to do things away from home? Have you had trouble maintaining physical effort for long periods? Have you been less able to complete tasks that require physical effort? Have you had trouble concentrating?* MFIS total score ranges from 0 to 20, with the following ranges reflecting how often the person is limited in activities by fatigue: 0–5 (never), 6–9 (rarely), 10–14 (sometimes), 15–19 (often) and 20 (almost always) (Chwastiak et al., 2005). The MFIS-5 is one of the components of the Multiple Sclerosis Quality of Life Inventory (MSQLI).

The mean score for the entire sample was 11.42, indicating that the people in our sample are "sometimes" limited by fatigue while conducting daily activities. A significant difference was also apparent between the MFIS-5 scores of men and women in our sample ($p < 0.05$). A graded relationship existed between severity of disease and fatigue, with those reporting mild MS, "rarely" limited by fatigue, while those with moderate and severe disability reporting they are "sometimes" and "often" limited by fatigue. The groups who reported having, or not having a relapse in the last year both appear to be "sometimes" affected by fatigue, however, those who had a relapse, on average scored 9% higher MFIS-5 scores; this difference was statistically significant ($p < 0.05$). In contrast, when we restrict the sample to those with RRMS only, significant differences were found between the relapse and the no relapse cohorts – those experiencing relapses scored 12.5% higher fatigue scores (10.2 v 11.4, $p<0.03$).

Figure 12. Modified Fatigue Impact Scale -5-Item Version (MFIS-5)

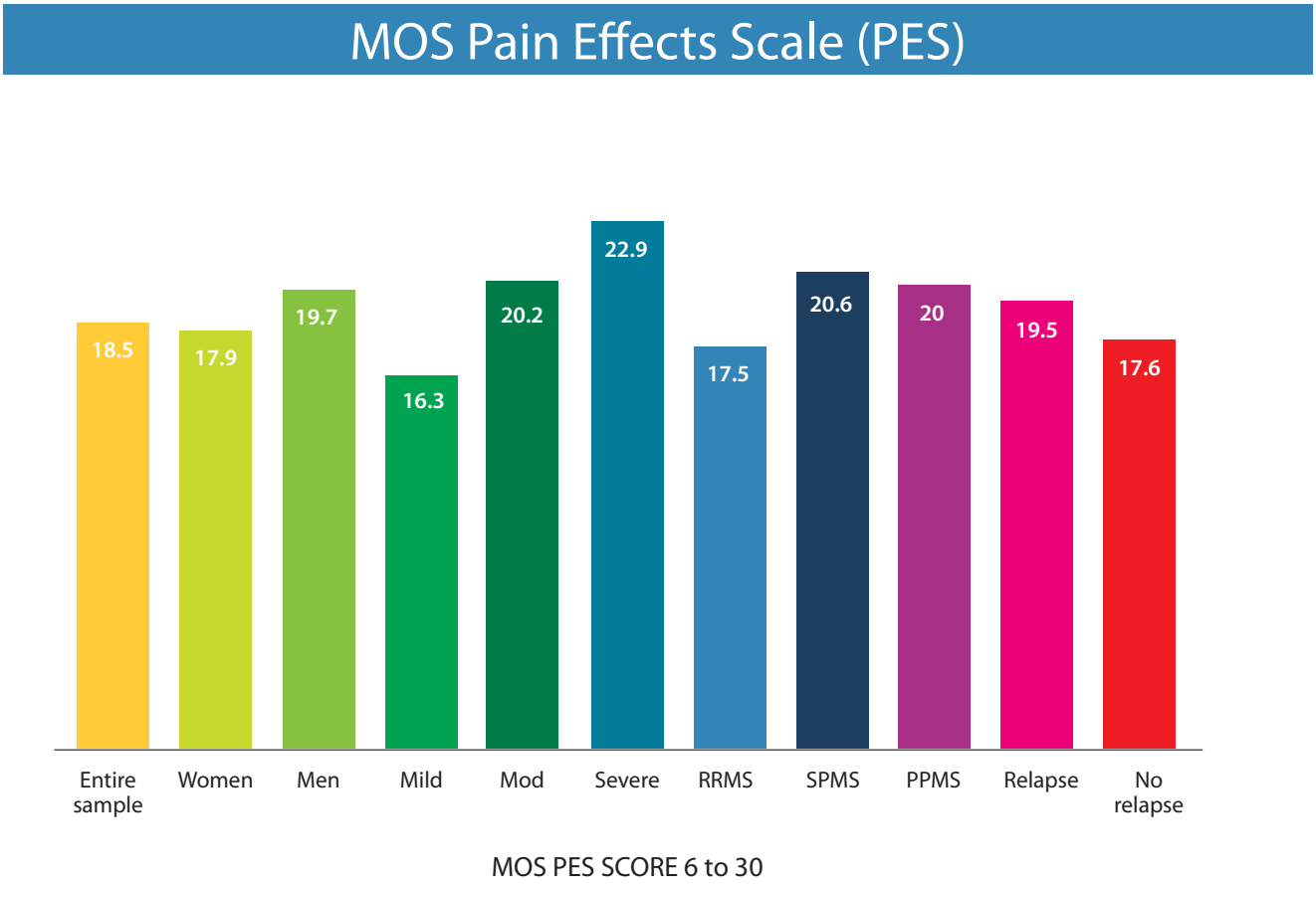


ii. Pain

The nature in which pain effects the lives of the people in our sample was assessed by the MOS Pain Effects Scale (PES). The PES is a modified form of the pain scale contained in the Medical Outcomes Study Functioning and Well-Being Profile. This instrument provides an assessment of the ways in which pain and unpleasant sensations symptomatic of their MS interfere with mood, ability to walk or move, sleep, work, recreation, and enjoyment of life. The PES consists of 6 items and the raw scores on the 6 items that constitute this scale are simply added to form a PES total score. Therefore, scores can range from 6-30. Items are scaled so that higher scores indicate a greater impact of pain on a person's mood and behaviour. PES total score ranges from 6 to 30, with the following ranges reflecting how often the person is limited in activities by pain: 6 to 12 (not at all), 12 to 18 (a little), 18-24 (moderately), 24-29 (quite a bit) and 30 (to an extreme degree). The PES is one of the components of the Multiple Sclerosis Quality of Life Inventory (MSQLI) (Ritvo et al., 1997).

The mean PES score in our sample was 18.46, indicating that unpleasant sensory symptoms such as pain and burning and tingling sensations "moderately" affected the people in our sample in their daily lives. Once more a graded relationship existed between severity of disability and PES score and significant differences were apparent between men and women, who reported being affected "a little" and "moderately" respectively ($p<0.05$). Significant differences also existed between those who had and those who did not have a relapse in the past year, also reporting "moderately" and "a little" respectively ($p<0.01$). This significant difference persisted when we restricted the analysis the RRMS group only with scores of 16.4 and 18.5 for the relapse and no relapse cohort respectively ($p<0.01$)

Figure 13. MOS Pain Effects Scale (PES)



7.2 Total costs: Direct, indirect and intangible costs

Direct costs constitute 31.2% of total costs and amount to €14,895 per person and year. Indirect costs represent 49.8% of total costs and are estimated as being €23,750 per person and year. Intangible costs calculated from QALY losses, are predicted to be €9,038– this

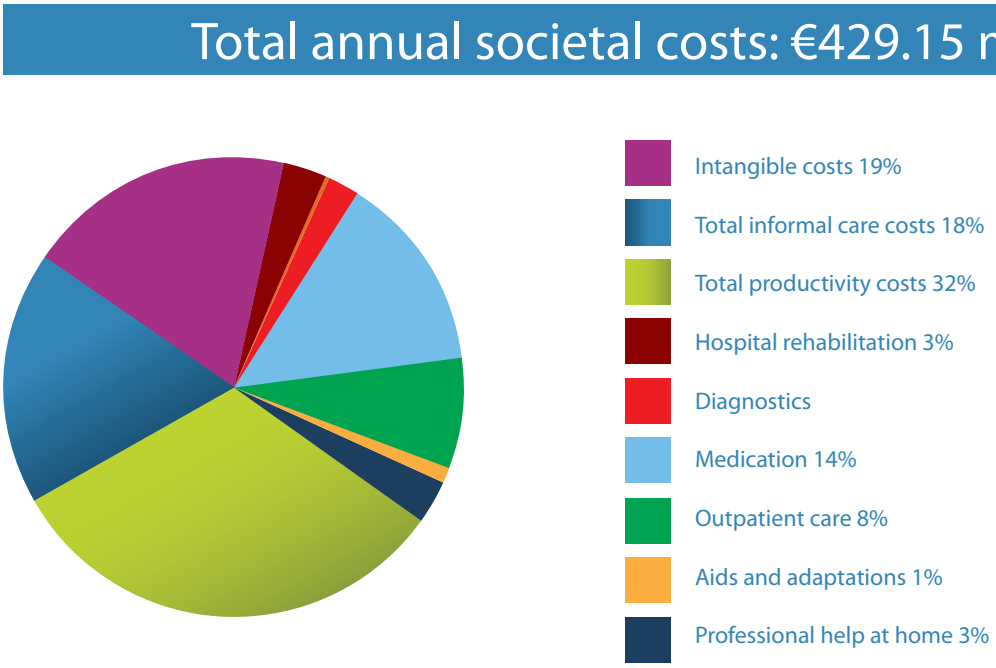
forms 18.9% of total costs. Costs attributed to productivity losses (€15,056) make up 31.5% of total costs, 60.1% of which are related to losses due to permanent withdrawal from the workforce due to MS. Informal care constitutes 18.1% of total costs and amount to €8,646 per person and per year. Total costs attributable to MS are estimated as being €47,683 per person, per year. ***Extrapolating costs from the study sample to the general population of people with MS in Ireland and assuming there are 9,000 people in Ireland with MS: national annual direct, indirect and intangible costs are estimated to be €134.1 million, €213.8 million and €81.3 million respectively. This provides for an overall total annual cost attributable to MS of €429.15 million.***

Figure 14. Total costs: Direct, indirect & intangible costs

Table 18. Total costs: Direct, indirect and intangible costs

Total annual costs	Societal costs per person €2014	Extrapolated costs (n=9,000) €2014
Direct costs		
Total direct medical	12,921	116,289,000
Total direct non-medical	1,974	17,766,000
Total direct costs	***14,895***	***134,055,000***
Indirect costs		-
Total productivity costs	15,056	135,504,000
Total informal care costs	8,646	77,814,000
Cost of depression	48.15	433,350
Total indirect costs	***23,750***	***213,751,350***
Total direct and indirect	***38,645***	***347,806,350***
Intangible costs	9,038	81,342,000
Total costs	***47,683***	***429,148,350***

Figure 15. Total annual costs by resource use: Direct, indirect and intangible costs



7.2.1 Total direct costs

The total direct costs per person with MS are estimated as being €14,895. Extrapolating from the study sample to the Irish population, assuming on overall MS prevalence of 9,000 people in Ireland – provides a total annual direct cost estimate of ***€134.1million***. Medication costs and costs attributable to outpatient care contribute the largest share to direct costs, 45% and 25% respectively, while hospital/rehabilitation costs constitute a further 10%. The remaining 30% is made up of costs attributable to formal care, diagnostics, aids and adaptations and nursing home/respite care (see Figure 16)

Figure 16. Direct costs of MS by resource use

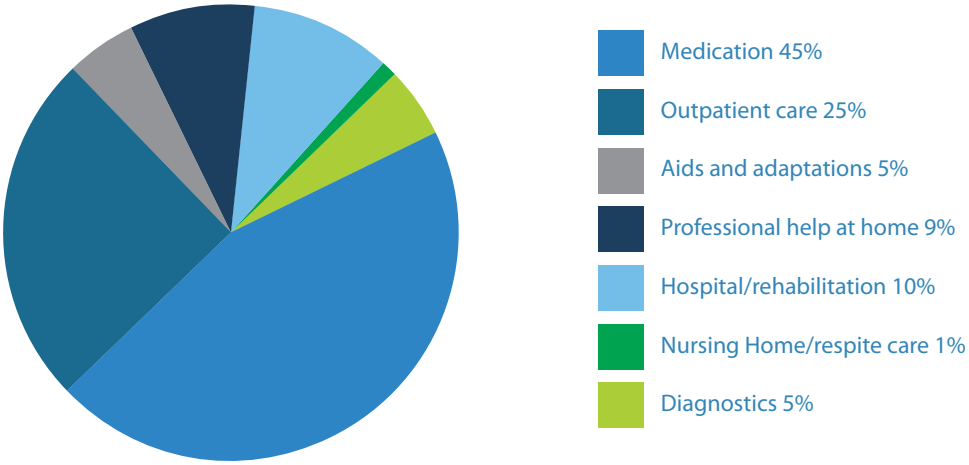


Table 19. Total direct costs, per person with MS and extrapolated costs

Column1	Average cost per person with MS	Extrapolated costs (n=9,000)
Hospital/rehabilitation	1,560	14,040,000
Nursing Home/respite care	173	1,557,000
Diagnostics	692	6,228,000
Medication	6,759	60,831,000
Outpatient care	3,737	33,633,000
Total direct medical costs	**12,921**	**116,289,000**
Aids and adaptations	687	6,183,000
Professional help at home	1,287	11,583,000
Total direct non-medical costs	**1,974**	**17,766,000**
Total direct costs	***14,895***	***134,055,000***

7.3 Direct healthcare resources (Client Service Receipt Inventory (CSRI))

Over 21% of our sample had stayed overnight in a hospital in the last year, on average each user stayed 8.6 nights and the mean across the entire sample was 1.8 nights; extrapolating this out to the national population with MS (n= 9,000), provides for an estimate of 16,409 nights spent in hospital by people with MS in Ireland.

On average 60% of our sample had 2 MRIs in the last year. The majority of our sample (83.5%) reported visiting a GP 7.2 times in the last year. So too with respect to neurologist visits, where 71.4% of our sample reported 3.4 consultations.

Investigations and tests were frequently reported by the study respondents, for example 67.2% reported having 4.4 blood tests in the last year; proportionately less reported visiting a physio, however, the mean usage for this group was high, at 14.6 visits per year. The use of formal care services such as HSE home help (7.2%), HSE Personal assistants (3.5%) and Private paid carers (5.4%), was less commonly reported by our study respondents, with annual hours of 312, 255 and 525, respectively.

Table 20. Direct resource use

Type of resource n=594	% Using resources	Annual mean per user	SD	Total units[15]: n=594	Total units[16]: n=9,000
Nights in hospital	21.2	8.6	10.0	1,083	16,409
Nursing home	0.7	126.5	167.2	526	7,970
Rehab centre	1.7	47.3	39.9	478	7,237
Respite centre	3.4	10.0	6.5	202	3,060
MRI	59.9	2.1	1.4	747	11,321
CAT scan	10.8	1.3	0.7	83	1,264
Blood tests	67.2	4.4	4.6	1,756	26,611
Lumber puncture or spinal tap	9.8	2.4	0.8	140	2,117
Neurology clinic or infusion site	61.8	5.2	5.6	1,909	28,922
Other outpatient	38.2	5	5.4	1,135	17,190
ED not overnight	6.6	2.6	1.4	102	1,544
GP	83.5	7.2	5.6	3,571	54,108
Neurologist	71.4	3.4	3	1,442	21,848
Otherdoctor eg. Cardiologist	17.2	4.4	3	450	6,811
Physio	40.4	14.6	12.2	3,504	53,086
Occupational therapist	15.7	7.4	11.2	690	10,456
Social worker	3.2	3.2	2.2	61	922
speech therapist	2.9	5.8	4.4	100	1,514
MS Ireland case worker	16.0	5.3	7.0	504	7,632
HSE home help (annual hours)*	7.2	312	317	13,344	202,176
HSE PA (annual hours)*	3.5	255	400	5,297	80,262
Private paid carers (annual hours)*	5.4	525	176	16,846	255,247
Aids and adaptations					
Wheelchair	20.1	1.0	n.a.	119	1,809
Crutches/Walking frame	30.6	1.0	n.a.	182	2,754
Home modifications	25.4	1.0	n.a	151	2,286
Medicalised bed	6.6	1.0	n.a	39	594
Vehicle modifications	25.9	1.0	n.a.	154	2,331

15. These figures represent the total resource in our study sample, annualised where necessary*.
16. These figures represent the total annual resource extrapolated to the national population of people with MS, assuming a total prevalence of 9,000.

7.4 Indirect costs

7.4.1 Total Indirect costs: Productivity losses, informal care & depression costs

Total annual indirect costs are estimated as being €23,750 per person with MS, extrapolated out to the national population with MS (n=9,000), provides for a total indirect cost estimate of €213.8 million. The factors contributing the largest proportion of indirect costs, were productivity losses accrued to having to permanently withdraw from the workforce due to MS (39%), this was followed by the hours of informal care provided to those with condition (36%). Presenteeism, which relates to lost productivity at work due to MS, constitutes 11% of total indirect costs and is higher than the estimates relating to absenteeism (6%) or officially reduced working weeks (8%).

Figure 17. Total indirect costs by constituent part

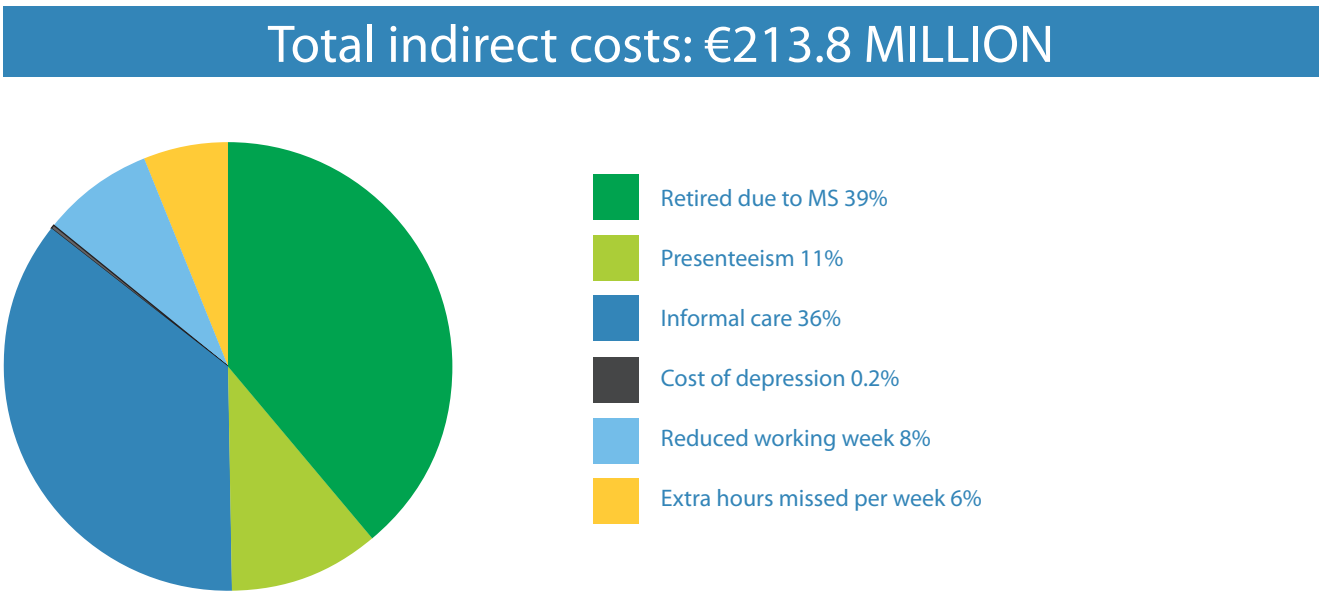


Table 21. Total Indirect costs: Productivity losses, informal care & depression costs

Productivity losses & Informal care	*Average costs per person with MS*	*Extrapolated costs (n=9,000)*
Officially reduced working week	1,846	16,614,000
Extra hours missed due to appointments, etc.	1,361	12,249,000
Retired early due to MS	9,173	82,557,000
Presenteeism	2,676	24,084,000
Total productivity losses	***15,056***	***135,504,000***
Informal care	***8,646***	***77,814,000***
Cost of depression	***48***	***433,350***
Total indirect costs	***23,750***	***213,751,350***

7.4.2 Productivity losses

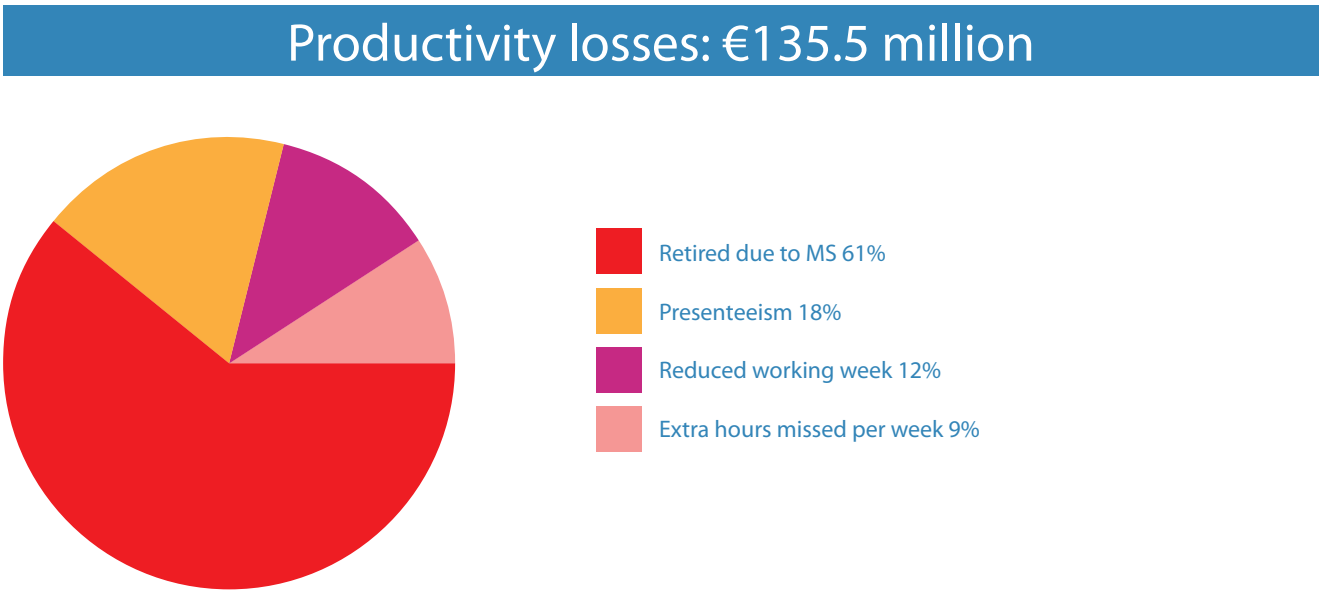
In our sample, 43.2% and 41.7% of women and men, respectively, were in paid employment. Of those in paid employment 35% of women and 29.6% of men had officially reduced their working week (women: 13 hrs, men: 10.8 hours). A smaller proportion reported missing extra hours due to appointments etc. in the last week: 20% of women missed 14.3 hours, while 25.6% of men reported missing 14.4 hours.

Presenteeism was an issue in the workplace in the previous week for 50% of women and 54% of men; women reported that MS affected their work performance by on average 18%, the equivalent figure for men was higher at 21%. This represents 18% of our total productivity losses and 11% of our total indirect costs. A considerable number of people in our sample reported having to permanently withdraw from the workforce due to their condition, in total 105 women and 57 men, which represents 27% of our entire sample; this represents 61% of our total productivity losses and 37% of our total indirect costs.

Table 24. The total number of work days lost due to MS, with respect to the headings discussed above are presented in Table 21. The total days lost reported by our sample was 61,372 and extrapolating to the national population with MS in Ireland, assuming a total prevalence of 9,000 people, provides an estimate of some 930,000 work-days lost due to MS annually.[17]

In our sample, (n=594) indirect costs attributable to productivity losses are estimated at being €15,056 per person. ***Extrapolating to the national population with MS in Ireland, assuming a total prevalence of 9,000 people, provides an estimate of total annual costs attributable to productivity losses of €135.5 million.***

Figure 18. Total productivity losses



7.4.3 Informal care

The majority of our respondents reported having received unpaid care from family or friends in the last week; in total, 63% received on average 15 hours of care in the previous week. In total, we estimate that there were 36,410 days of care provided to our sample respondents, extrapolating this out to the national population of those with MS, assuming a total prevalence of 9,000 people, provides for an estimate of 551,680 days of care provided by the family and friends of those with MS. For the purpose of this cost-of illness study and to ensure a more conservative estimate caregiving hours were capped at a maximum of 40 hours per week. Doing so reduced the weekly hours of informal care to 12 hours

17. These figures were calculated by assuming an 8 hour day for officially reduced working weeks and absenteeism and 240 working days per year with respect to presenteeism and for those permanently withdrawing from the work-force.

Our estimate for informal care forms 35% of our total indirect costs. In our sample, (n=594) indirect costs attributable to informal care estimate is €8,646 per person. ***Extrapolating to the national population with MS in Ireland, assuming a total prevalence of 9,000 people, provides an estimate of total annual costs attributable to informal care of €77.8 million***

Table 22. Productivity losses & informal care

Employment variables	%	Mean in recall period (SD)	Total hours annually	Unit Costs €2014	Total Costs €2014
Women (n=424)					
Officially reduced working week (hrs per week)	15.1	13 (4.6)	39,862	21.3	849,061
Extra hours missed in the last week (due to appointments, etc.)	8.5	14.3 (12.9)	24,720	21.3	526,536
Retired early due to MS	24.7	n.a.	n.a.	29,848.	3,134,040
Presenteeism (% of work performance affected)	43.2	18.1 (25.3)	n.a.	29,848	988,655
Men (n=170)					
Officially reduced working week (hrs per week)	12.4	10.8 (5.1)	10,942	22.6	247,727
Extra hours missed in the last week (due to appointments, etc.)	25.4	14.4 (14.3)	12,476	22.6	282,457
Retired early due to MS	33.5	n.a.	n.a.	40,611	2,314,827
Presenteeism (% of work performance affected)	41.8	20.8 (45.5)	n.a.	40,611	599,743
Total productivity losses *(Per person with MS)*					**8,943,046** ***(15,056)***
Informal care					
Weekly hours of informal care provided *(Per person with MS)*	63	12 (11.4)	233,030	22.0	5,135,981 ***(8,646)***
Total productivity & informal care costs *(Per person with MS)*					***14,079,027*** ***(23,702)***

Table 23. Extrapolated Productivity & Informal care costs

Productivity losses & Informal care	*Total Costs*	*Average costs per person with MS*	*Extrapolated costs (n=9,000)*
Officially reduced working week	1,096,787	1,846	16,614,000
Extra hours missed due to appointments, etc.	808,993	1,361	12,249,000
Retired due to MS	5,448,867	9,173	82,557,000
Presenteeism	1,588,399	2,676	24,084,000
Total productivity losses	***8,943,046***	***15,056***	***135,504,000***
Informal care	***5,135,981***	***8,646***	***77,814,000***
Total productivity & informal care costs		***23,702***	***213,318,000***

Table 24. Total number of work days lost due to MS & total days of care provided

Employment variables	Days lost per year (Study sample, n=594)	Days lost per year (Extrapolated, n=9,000)
Officially reduced working week	6,351	96,220
Extra days missed in the last week, due to appointments, etc.	4,650	70,447
Retired early due to MS	38,868	588,909
Presenteeism	11,504	174,305
Total number of work days lost due to MS	***61,372***	***929,881***
Informal care: total annual days of care provided	***36,410***	***551,680***

7.4.4 Depression and Anxiety

A total of 229 people in our sample have since the onset of MS had been treated for depression or anxiety or both, representing 38.55% of our total sample. There was a degree of heterogeneity within our sample when it came to the diagnosis of depression or anxiety (see Fig 15 & Fig 16). The strongest predictor of a diagnosis of depression and anxiety in our sample was whether the person had experienced a relapse in the past year. Those who reported having a relapse were 47% and 41% more likely to report a depression ($p<0.001$) or anxiety ($p<0.05$) diagnosis respectively. Significant differences were found also between those with mild MS and severe MS regarding a diagnosis of anxiety with 24.1% and 47.4% reporting a diagnosis respectively ($p<0.001$). While similar significant differences were found between those with RRMS and SPMS and with SPMS and PPMS with respect to an anxiety diagnosis; the mean rate of anxiety diagnosis for those with SPMS represents a 45% increase over that reported for those with RRMS ($p<0.05$). While those with SPMS also more likely than those with PPMS to have an anxiety diagnosis with a mean difference of nearly 18% ($p<0.05$). A graded but non-significant relationship existed between disability severity and a depression diagnosis.

In the general population the annual prevalence of mental health problems including depression and anxiety is estimated as being 10% (Doherty et al., 2007). However, as our estimate was not a one year prevalence estimate, we assumed, as was reported in Koch et al. (2008), that two-thirds would report depressive symptomology in the previous year. This gave us of a figure of 15% of our sample population who would be free of depression and/or anxiety if the prevalence rates in the MS population were analogous to that of the general population. Assuming 3.3 and 0.7 extra GP visits per year and medication costs of €202.25 and €8.43 for depression and anxiety respectively (Doherty et al., 2007), we estimate the annual direct cost of depression (GP and medication use) as being €321 per person. Extrapolating to the broader MS population and specifically to the excess prevalence of depression within the broader MS population; we estimate the excess cost of depression in the MS population as being in the region of €433,350 per year.

Figure 19. Depression – sample breakdown

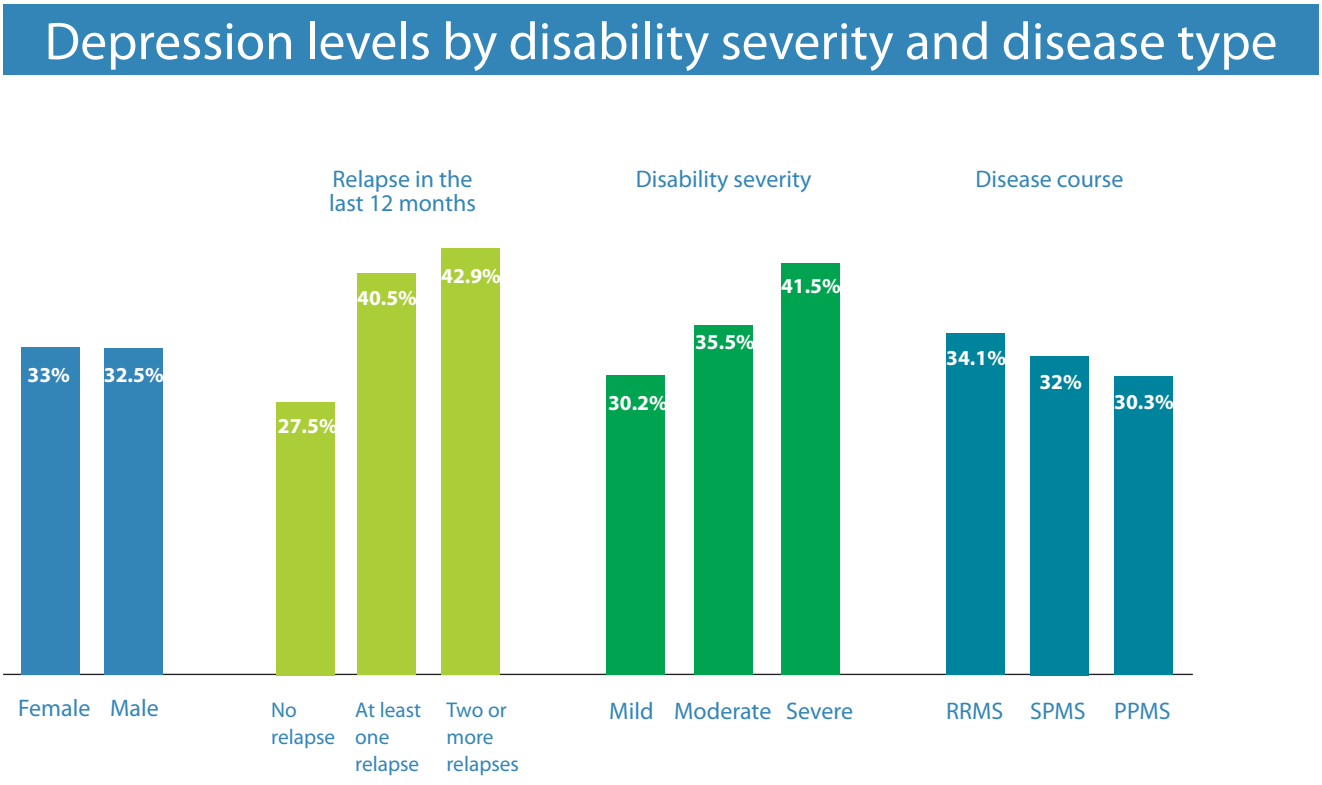
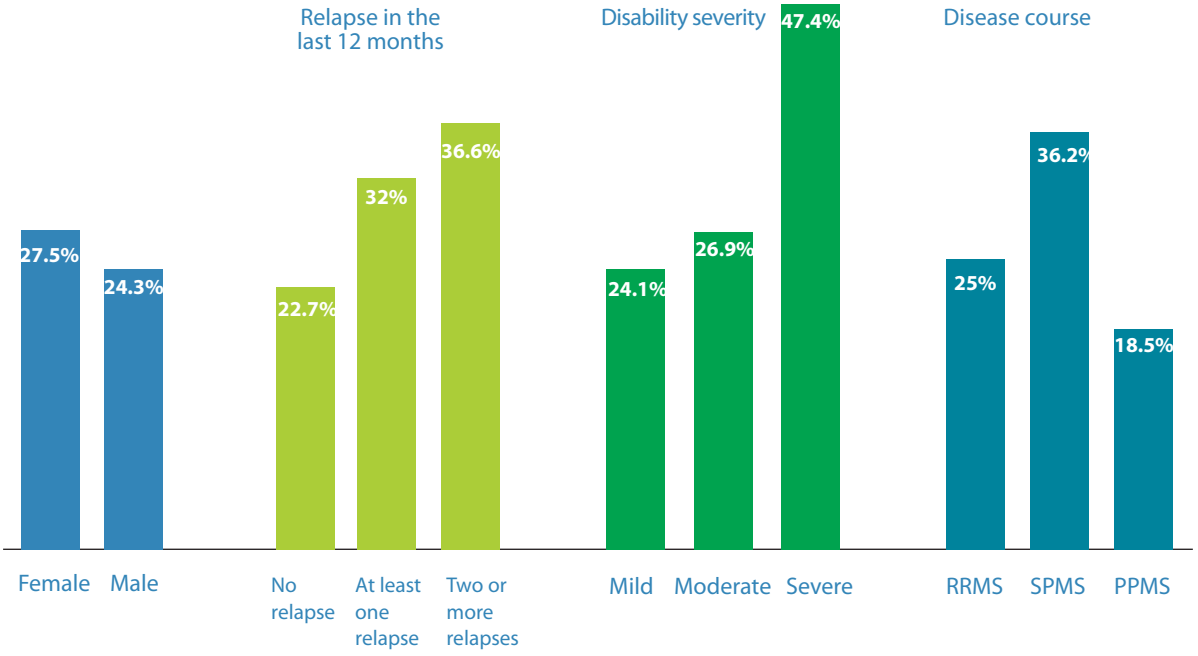


Figure 20. Anxiety – sample breakdown



7.4.5 Intangible costs (QALYs lost)

Intangible costs are costs that can be attributed to 'goods' for which there is no market yet but where there is a willingness to pay. In this case, the study respondents were asked about their *health-related quality of life (HRQoL),* under the following domains: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Subsequently, the difference between the HRQoL scores reported by the study respondents and an age- and sex-matched sample from the UK general population,[18] were calculated (Kind et al., 1999). This method generates an estimate of the number of quality-adjusted life-years (QALYs) lost by the MS sample in one year.

The cohort of 541 people experienced a total loss of 150.46 QALYs due to MS during the year, or an average of 0.278 QALYs per person and year (0.353 for men, 0.248 for women). The current guidelines with respect to threshold or willingness-to-pay for a unit of effect (life year or QALY) in Ireland, lies between €20,000 and €45,000 per QALY. Using these values for a QALY lost, intangible costs for MS in Ireland are calculated as being in the range of €5,562 to €12,515 per person and year; the mid-point of which: €9,038, will be used as the estimate for the purpose of this study.

18. Although work is underway, currently no such values exist for the general ROI population.

Table 25. QALYs lost (women)

Age group	Mean utility (UK population)	Mean utility (sample)	Difference	No. of respondents	QALYs lost
under 25	0.94	0.71	0.23	8	1.87
25-34	0.93	0.75	0.18	60	10.56
35-44	0.91	0.67	0.24	106	25.78
45-54	0.85	0.60	0.25	107	26.34
55-64	0.81	0.55	0.26	76	19.53
65-74	0.78	0.36	0.42	27	11.40
75+	0.71	0.55	0.16	2	0.32
Total	n.a.	n.a	n.a.	386	95.80

Table 26. QALYs lost (men)

Age group	Mean utility (UK population)	Mean utility (sample)	Difference	No. of respondents	QALYs lost
under 25	0.94	0.74	0.20	2	0.40
25-34	0.93	0.61	0.32	14	4.51
35-44	0.91	0.58	0.33	43	14.05
45-54	0.85	0.50	0.35	55	19.52
55-64	0.80	0.42	0.38	29	11.03
65-74	0.78	0.39	0.40	11	4.35
75+	0.73	-0.07	0.80	1	0.80
Total	n.a.	n.a	n.a.	155	54.66

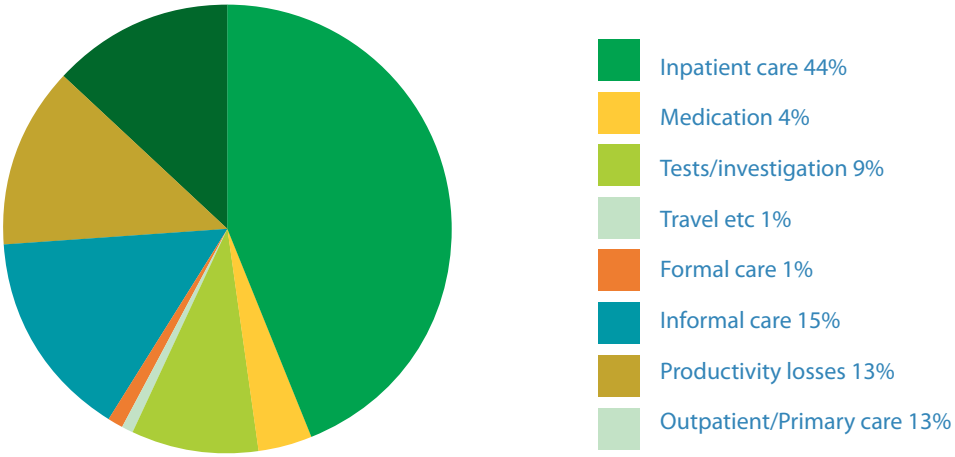
7.5 Costs of MS relapse

7.5.1 Total annual cost of MS relapses in Ireland.

We estimate the direct and indirect costs associated with a single relapse in Ireland at €1,715 and €723, respectively. This provides for a total estimate of €2,438 for a single relapse. Of those who reported relapses in the last year, the average number of per person was 1.85, therefore we estimate the annual cost of relapses in Ireland as being €4,510 per person; this figure is comprised of annual direct costs of €3,173 and indirect costs of €1,337. We extrapolate these figures to the broader population by assuming a total prevalence of 9,000 people with MS and as 41.8% of our sample had a relapse in the last year, we assume the same for the national population. ***Therefore we estimate the total annual direct and indirect costs of MS relapse as being €11.8 million and €5.1 million, respectively. This provides a total annual cost attributable to MS relapse of €16.9million.***

Figure 21. Total annual cost of relapse

Total annual cost of relapse: €16.9 million



7.5.2 Direct costs associated with a relapse

In total 41.2% (n=247) of our sample reported having a relapse in the previous year. On average those reporting relapses had 1.85 relapses in the last year. The GP was the most frequently utilised medical service with 47% of our sample reporting ringing or visiting a GP as a result of their last relapse. 18% reported being admitted to hospital, this cost constitutes 62% of the total direct costs attributable to a single relapse. The total direct cost of a relapse estimated was €423,703 and this equates to €1,715 per person in our sample who reported having a relapse.

Figure 22. MS relapse: Direct costs

MS relapse direct costs: €1,715

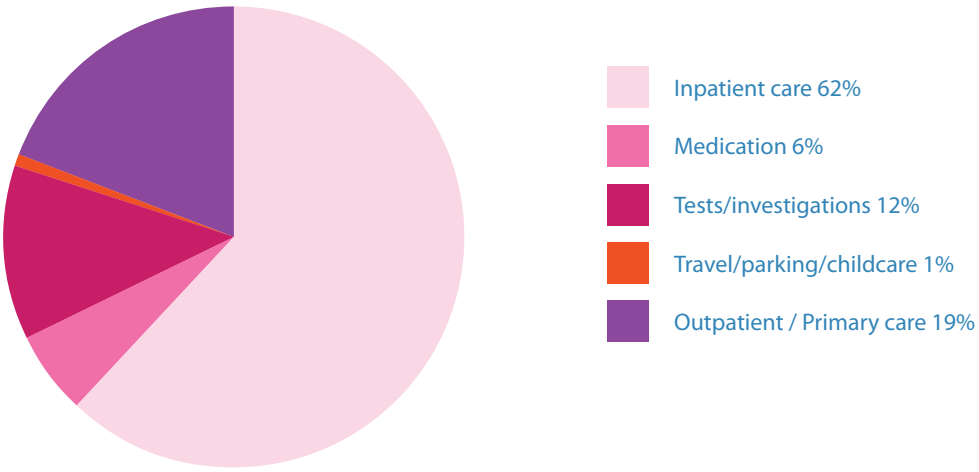


Table 27. Direct costs of a relapse

Medical costs of relapses (n=247)	% of sample n, (%)	Mean (SE)	Total units	€ Cost	€ Total
Rang/visited nurse	59 (23.9)	1	59	31.6	1,864
Rang/visited GP	113 (45.8)	1	113	46.2	5,227
Physio	37 (14.9)	1	37	31.6	1,169
Attended ED	31 (12.5)	1	31	268	8,308
Neurology clinic	75 (30.4)	1	75	824	61,800
Admitted to hospital	45 (18.2)	1	45	5,829	262,326
Additional treatment received					
Low intensity	125 (50.6)	n.a.	125	8	1,000
Moderate intensity	77 (31.2)	n.a.	77	58	4,466
High intensity	45 (18.2)	n.a.	45	440	19,800
Tests or investigations					
Blood test	117 (47.37)	1	117	8.33	975
MRI scan	91 (36.84)	1	91	507	46,181
Spinal tap	13 (5.26)	1	13	227	2,951
OT/Physio assessment	59 (23.89)	1	59	31.6	1,864
Other costs					
Travel (hrs)	91 (36.84)	3.22 (2.24)	293	13.27	3,890
Parking (hrs)	79 (31.98)	3.94 (2.09)	311.3	1.8	560
Childcare (hrs)	10 (4.04)	6.00 (2.11)	60	22.04	1,322
Total					***423,703***
Total per person who reported a relapse in the past year (n=247)					***1,715***

7.5.3 Indirect costs associated with a relapse

In total 60% of our sample reported requiring extra informal care as a consequence of their last relapse, while 14% received extra hours of formal care. The most common type of informal care provided was home-help, which represented 38% of total hours of care provided. Total indirect costs associated with a relapse are estimated as being €178,523 which equates to €723 per person who reported having a relapse in the past year.

Figure 23. MS relapse: Indirect costs

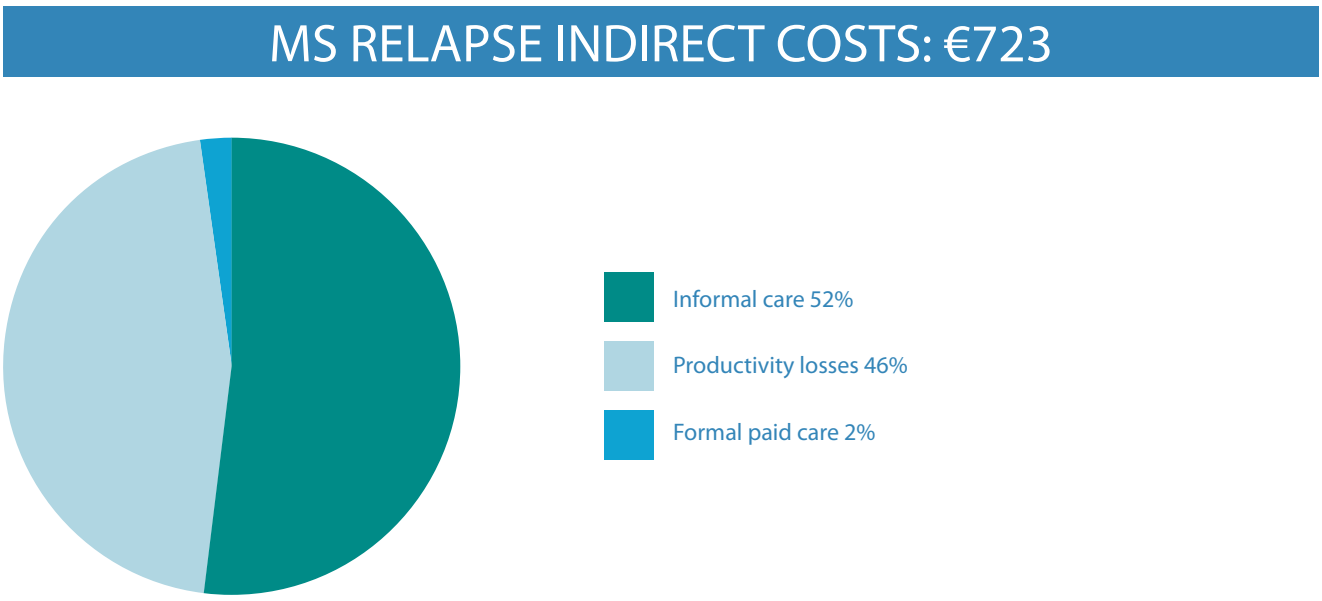


Table 28. Indirect costs associated with a relapse

Resource use	Sample, n (%)	Mean (SE)	Total units	€ Cost	€ Total
Care needs					
Extra hours of paid care	14 (5.67)	13.2 (11.42)	185	20.7	3,828
Informal care					
Personal care (hrs)	38 (12.14)	11.7 (12.85)	445	22.04	9,799
Home help (hrs)	117 (47.36)	13.8 (18.45)	1,619	22.04	35,689
Help outside home (hrs)	106 (42.91)	7.8 (11.98)	826	22.04	18,199
Transport (hrs)	88 (35.62)	8.7 (8.68)	760	22.04	16,757
Other tasks (hrs)	49 (19.83)	12.1(18.99)	595	22.04	13,122
Total hrs of unpaid care			4,245	22.04	93,566
Impact of relapse on productivity, n=93					
Time spent of sick	52 (21.05)	8.4 (7.08)	435	22.04	9,593
Unable to return to work	2 (0.008)			35,768	71,536
Total					***178,253***
Total per person with active MS					***723***

7.6 Resource use by disability severity

7.6.1 Direct resource use by disability severity

Approximately 20% of respondents with mild MS reported receiving inpatient care in hospitals, compared with 22% with moderate MS and 32% with severe MS. The number of days of inpatient stays in hospitals increased with disability severity and significant differences were apparent when comparing those with mild (7.3 days) and moderate MS (9.8 days) and between those with mild (7.3 days) and severe MS (11.2 days), ($p < 0.05$).

Four people in our sample reported requiring nursing home care, of those who did so, 3 had severe MS and one was in the moderate MS subgroup. Few people reported requiring respite care in the last year: 1.8% of the mild subgroup reported approximately 8 visits in the last year while those with moderate and severe MS, 2.8% and 14.6% had 7 and 15 visits, respectively; those with severe MS had significantly more visits than the other two subgroups ($p<0.05$).

Investigations and tests were frequently reported by the study respondents, across all levels of disability severity, for example, 64% of respondents with mild MS, 56% of those with moderate MS and 45% of those with severe MS, reported having had an MRI in the last year.

More than 80% of those with mild, moderate and severe MS reported seeing a GP in the last year, and the frequency of visits were similar across the disability severity categories, those with mild and moderate MS detailing 7.2 visits, while those with severe MS reporting 7.8 visits. These similarities persisted with respect to visits to a neurology clinic, emergency department visits and appointments with other clinicians such as cardiologists.

A graded significant relationship existed between disability severity and physiotherapy visits: those with severe MS reported having 10 physiotherapist sessions in the previous six months, three and four sessions more than those with moderate and mild disability, respectively ($p<0.05$).

With regard to formal care, a greater proportion of those with severe disability reported requiring extra formal care such as HSE home help, HSE personal assistants and private paid carers than those with mild or moderate MS. In the case of HSE home help, 41.5% of those in the severe category reported receiving 10 hours of this service in the previous week, while 12.3% of those in the moderate group reported 3.7 hours ($p<0.05$); zero of the mild MS subgroup reported utilising this service.

The degree to which the respondents reported requiring specific aids and adaptations due to their condition was also associated with disability severity. In each category, significant differences were apparent across the spectrum of disability severity, for example 71% of those with severe disability reported having home adaptations, while 46% and 11% reported same in the moderate and mild groups, respectively.

Table 28. Direct resource use by disability severity

	Mild (n=342)		*Moderate (n=211)*		*Severe (n=41)*	
Type of resource	***% Using***	***Mean (SD)***	***% Using***	***Mean (SD)***	***Obs %***	***Mean (SD)***
Hospital	19.6	7.3 (10.1)	21.8	9.8* (10.3)	31.7	11.2† (7.5)
Nursing home	0	0 (0)	0.5	7 (.)	7.3	166.3 (180)
Rehab centre	0	0 (0)	2.8	42.7 (41.9)	9.8	54.3 (41.9)
Respite centre	1.8	7.7 (4.5)	3.8	7.2 (2.8)	14.6	16 † ‡ (8.2)
MRI	64.0	2.1 (1.4)	55.9	2.1 (1.4)	46.3	1.9 (1.1)
CAT scan	10.8	1.2 (0.7)	9.5	1.2 (0.3)	17.1	1.6 (1.1)
Blood tests	71.6	4.1 (3.7)	62.6	4.6 (5.5)	53.7	6.5 † (6.9)
Lumber puncture	12.0	1.3 (1)	7.6	1.1 (0.1)	2.4	1 (.)
Neurology clinic or infusion site	64.9	5.2 (6)	55.9	5.2 (5)	65.9	4.8 (4.2)
Other outpatient	35.7	4.8 (5.8)	42.2	4.8 (4.8)	39	6.2 (6.8)
ED not overnight	6.4	2.4 (1.4)	6.2	3 (1.6)	9.8	2.6 (1.0)
GP	83.9	7.2 (6)	83.4	7.2 (4.8)	80.5	7.8 (6.6)
Neurologist	75.4	3.4 (2.6)	65.4	3.6 (3.2)	68.3	3.8 (5.4)
Otherdoctor eg. Cardiologist	15.5	4.2 (2.8)	18.5	4.4 (2.6)	24.4	4.2 (5.6)
Physio	28.4	12.6 (9.8)	56.4	14.8 (10.8)	58.5	20.8 (24.5)
OT	7.3	4.8 (3.4)	22.7	6 (4.4)	48.8	14 † ‡ (21.8)
Social worker	1.5	3.2 (1)	4.7	3.6 (3)	9.8	2.6 (1.0)
Speech therapist	0.6	4 (2.8)	4.7	5.6 (4.6)	12.2	7.2 (5.4)
Medication	100		100		100	
MS Ireland case worker	12.3	10.4 (15.2)	20.4	9.4 (12.8)	24.4	13 (14.8)
HSE home help (weekly hrs)	.	.	12.3	3.7 (3.1)	41.5	10.0 ‡ (3.1)
HSE PA (weekly hrs)	0.1	6 (2.8)	4.3	4.9 (3.4)	24.4	3.5 (3.6)
Private paid carers (weekly hrs)	0.03	6 (.)	8.1	7.9 (5.1)	34.1	13.0 (5.1)
Aids and adaptations						
Wheelchair	5.8	5.8	32.7	32.7*	73.2	73.2† ‡
Crutches	13.7	13.7	55.9	55.9*	41.5	41.5† ‡
Walking Frame	2	2	29.4	29.4*	46.3	46.3† ‡
Home modifications	10.5	10.5	45.9	45.9*	70.7	70.7† ‡
Medicalised bed	0.6	0.6	7.6	7.6*	51.2	51.2† ‡
Vehicle modification passenger	1.8	1.8	9.5	9.5*	41.5	41.5 † ‡
Vehicle modification driver	7.0	7.0	36.9	36.9*	22.9	22.9 † ‡

*Difference is statistically significant compared to the mild subgroup (p-value<0.05)

† Difference is statistically significant compared to the mild subgroup (p-value<0.05)

‡ Difference is statistically significant compared to the moderate sub-group (p-value<0.05)

‡ Difference is statistically significant compared to the moderate sub-group of patients (p-value<0.05)

7.6.2 Indirect resource use by disability severity

As is the case in previous studies in, we found that in most cases, indirect resource use increased as disability severity progresses. As a case in point, a graded significant relationship existed between disability severity and employment status; those with mild MS are more than twice as likely as those with moderate disability to be in paid employment, while a similar relationship exists when comparing those with moderate and severe disability, with employment rates of 26% and 15%, respectively. Permanent withdrawal from the workforce due to MS is also predicted by disability severity; approaching 66% of those in the severe subgroup reported retiring as a result of their condition, this figure falls significantly when examining the moderate (39.8%) and mild subgroups (15.6%). Significant differences were also apparent when it came to hours of informal care received in the previous week, those with severe MS requiring 2.7 times as many hours care than those with mild disability. While those with moderate MS reporting 56% more hours of informal care than those with mild MS and 40% less than those with severe MS.

Table 29. Indirect costs by disability severity

	Mild (n=342)		Moderate (n=211)		Severe (n=41)	
Employment variables	Obs %	Mean (SD)	Obs %	Mean (SD)	Obs %	Mean (SD)
In paid employment	56.4	56.4	26.1	26.1*	15.0	15
Full time (over 30 hours)	43.3	43.3	16.6	16.6	15	15†
Officially reduced working week (hrs per week)	16.0	12.1 (4.9)	13.7	13.0 (4.5)	2.4	10
Extra hours missed in the last week	9.6	13.3 (11.7)	8.5	16.9 (14.5)	7.3	10
Retired due to MS	14.9	14.9	39.8	39.8*	65.8	65.8†‡
Presenteeism (% of work performance affected)	25.4	14.7 (2.3)	26.1	33.8* (34.5)	14.6	18.3 (16.0)
Informal care						
Weekly hours of informal care received	47.4	8.7 (9.6)	83.4	13.2* (10.7)	85.3	21.8†‡ (15)

*Difference is statistically significant compared to the mild subgroup (p-value<0.05)

† Difference is statistically significant compared to the mild subgroup (p-value<0.05)

‡ Difference is statistically significant compared to the moderate sub-group (p-value<0.05)

‡ Difference is statistically significant compared to the moderate sub-group of patients (p-value<0.05)

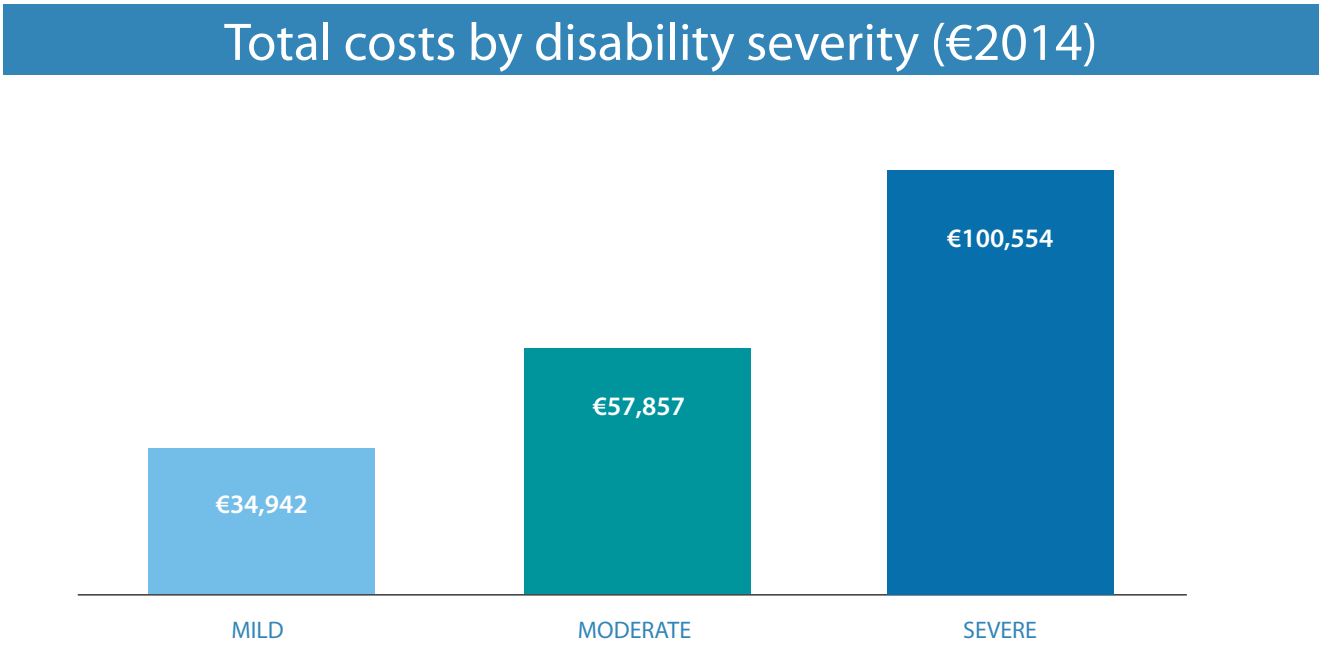
7.7 Costs by disability severity

As in previous studies, costs increase as disability increases, and QoL decreases as the disease progresses. In order to make our results comparable to published studies, results are presented for those with mild, moderate and severe MS. Within each group, indirect costs attributable to MS, form a larger share of total costs than direct costs (see Figure 1). The relative contributions of the cost components however, differed among the subgroups; for example, indirect costs comprised a larger proportion of total costs in moderate compared to both mild and severe disability subgroups (56% for moderate and 46% for both mild and severe). While for those with mild MS, direct costs (36%) comprised a larger proportion than those in the moderate (24%) or severe groups (26%). There is a graded relationship between disability severity and intangible costs, those with intangible costs composing 15%, 20% and 28% for those with mild, moderate and severe MS, respectively.

Table 30. Costs by disability severity (per person and year)

Disability level	Direct costs	Total indirect costs	Productivity costs	Informal care costs	Utilities EQ-5D	Intangible costs	Total costs (€, 2014)
Mild (57.6%)	14,269	15,470	10,773	4,697	0.718	5,202	34,942
Moderate (35.2%)	13,696	32,671	20,088	12,583	0.492	11,490	57,857
Severe (6.9%)	26,298	46,223	24,851	21,372	-0.027	28,033	100,554

Figure 24. Total costs by disability severity, per person and year.



7.8 Resource use by disease course (RRMS, SPMS, PPMS)

7.8.1 Direct resource use by disease course (RRMS, SPMS & PPMS)

The varying care needs of people with different forms of MS are explored in this section. Approximately 20% of respondents with RRMS reported receiving inpatient care in acute hospitals, compared with 24% with SPMS and 26% with PPMS. The number of days of inpatient stays in hospitals varied across the disease types with those with RRMS, SPMS and PPMS reporting 7.2, 11.2 and 9.6 nights in hospital respectively

Two people with SPMS reported requiring nursing home care, while the need for such care was not reported for those with the other two disease types.

Few people reported requiring respite care in the last year: 1.6% of the RRMS reported 8 visits in the last year while those with SPMS and PPMS, 6.2% and 9.1% had 9 and 15 visits, respectively. Investigations and tests were frequently reported by the study respondents, across the disease course spectrum, for example, 67.9% of respondents with RRMS, 49.5% of those with SPMS and 37.9% of those with PPMS, reported having had an MRI in the last year.

More than 80% of those with RRMS, SPMS and PPMS MS reported seeing a GP in the last year, and the frequency of visits were similar

across the disease course spectrum, those with RRMS and PPMS detailing 7 visits, while those with SPMS reporting 7.6 visits.

32% of those with SPMS reported seeing an occupational therapist (OT) 5.2 times in the previous year, while 11.2% and 22.7% of those with RRMS and PPMS reported 5 and 9.4 visits respectively.

With regard to formal care provision, a greater proportion of those with SPMS reported utilising HSE home help (19.6%, 8.6 hours per week), compared to those with RRMS (2.9%, 3.4 hours per week) and those with PPMS (13.6%, 4.8 hours per week). A similar pattern emerged with respect to private paid care, with a larger proportion of those with SPMS (18.6%, 6.2 hours per week) using this service, compared to those with RRMS (1.6%, 6.6 hours per week) and those with PPMS (10.1%), although those with PPMS reporting utilising more hours per week (15.9).

The degree to which the respondents reported requiring specific *aids and adaptations* due to their condition was also associated with disease type. In each category of *aids and adaptations,* those with SPMS and PPMS reported significantly higher usage than those with RRMS. However, there was no significant differences between the SPMS and the PPMS categories however. As a case in point, 19% of those with RRMS reported having had home modifications, while for those in the SPMS and PPMS categories, the proportions were 50.5% and 51.5%, respectively.

7.8.2 Direct resource use by disease course (RRMS, SPMS & PPMS)

Table 31. Direct resource use by disease course (RRMS, SPMS & PPMS)

	RRMS (N=374)		SPMS (n=97)		PPMS (n=66)	
Type of resource	***% Using***	***Mean (SD)***	***% Using***	***Mean (SD)***	***% Using***	***Mean (SD)***
Hospital	20.1	7.2 (8.1)	23.7	11.2 (12.7)	25.8	9.6 (7.3)
Nursing home	0	0 (0)	2.1	10.5 (4.9)	0	0
Rehab centre	1.1	25.5 (20.3)	3.1	67 (40.7)	3	76 (65.1)
Respite centre	1.6	8 (4.0)	6.2	9.0 (3.7)	9.1	14.7 (9.1)
MRI	67.9	2.0 (1.32)	49.5	2.2 (1.5)	37.9	1.8 (0.7)
CAT scan	10.2	1.1 (0.3)	14.4	1.4* (0.8)	1.5	1.3 (0)
Blood tests	74.1	4.4 (4.6)	56.7	4.0 (3.6)	46.9	4.8 (5.4)
Lumber puncture	10.7	1.2 (1.0)	3.1	1.1 (0.1)	6.1	1.2 (0.1)
Neurology clinic	65.2	5.4 (6.2)	56.7	5.2 (5.0)	51.5	4.4 (4.6)
Other outpatient	37.7	5.0 (6.2)	35.1	5.4(5.0)	42.4	4.0 (3.0)
ED not overnight	6.4	2.4 (1.0)	6.2	2.2 (0.8)	6.1	3 (1.0)
GP	85.6	7 (5.0)	83.5	7.6 (5.8)	81.8	7 (6.0)
Neurologist	74	3.8 (3.6)	67	3.2 (1.6)	63.6	2.6 † (1.0)
Otherdoctor eg. Cardiologist	17.9	4.2 (3.2)	15.5	3.8 (2.2)	15.2	4.2 (2.0)
Physio	35	13.6 (9.8)	61.9	13.8 (9.8)	48.5	15.2 (13.2)
OT	11.2	5 (3.8)	32	5 (3.0)	22.7	9.4 † ‡ (6.4)
Social worker	1.8	3.8 (3.6)	10.3	2.6 (0.8)	0	0

Speech therapist	1.6	6.2 (5.2)	7.3	6.2 (5.0)	6.1	4.4 (3.0)
Medication	100		100		100	
MS Ireland case worker months	14.9	10 (13.4)	23.7	11.8 (15.4)	13.7	4.2 (3.8)
HSE home help (weekly hrs)	2.9	3.4 (2.8)	19.6	8.1 (7.7)	13.6	4.8 (4.0)
HSE PA (weekly hrs)	1.3	4.2 (2.8)	5.2	6.2 (4.3)	15.1	3.8 (3.2)
Private paid carers (weekly hrs)	1.6	6.6 (2.7)	18.6	6.2 (4.3)	10.1	15.9 (12.8)
Aids and adaptations						
Wheelchair	10.2	10.2 (n.a)	43.3	43.3* (n.a.)	48.8	48.8 † (n.a.)
Crutches	23.8	23.8 (n.a.)	52.6	52.6* (n.a.)	50	50 † (n.a.)
Walking Frame	6	6 (n.a.)	43.2	43.3* (n.a.)	30.3	30.3 † (n.a.)
Home modifications	19	19 (n.a.)	50.5	50.5* (n.a.)	51.5	51.5 † (n.a.)
Medicalised bed	1.6	1.6 (n.a.)	15.5	15.5* (n.a.)	19.6	19.6 † (n.a.)
Vehicle modification passenger	3.2	3.2 (n.a.)	13.4	13.4* (n.a.)	22.7	22.7 † (n.a.)
Vehicle modification driver	12.8	12.8 (n.a.)	36.1	36.1* (n.a.)	30.3	30.3 † (n.a.)

7.8.3 Indirect resource use by disease course (RRMS, SPMS & PPMS)

A significant relationship existed between type of MS and employment status; 51% of those with RRMS were in paid employment, while for those with SPMS and PPMS fewer were working at the time of the survey; 21.8% and 27.2% respectively.

Permanent withdrawal from the workforce due to MS is also predicted by disease type; approaching 55% of those with SPMS reported retiring as a result of their condition, this figure falls significantly when examining the PPMS (36.4%) and RRMS subgroups (18.5%). Significant differences were also apparent when it came to hours of informal care received in the previous week, those with RRMS reporting receiving 45% and 42% less hours of care, compared to those with SPMS and PPMS, respectively.

Table 32. Indirect resource use by disease course (RRMS, SPMS & PPMS)

	RRMS (n=374)		SPMS (n=97)		PPMS (n=66)	
Employment variables	Obs %	Mean (SD)	Obs %	Mean (SD)	Obs %	Mean (SD)
In paid employment	51.1	51.1	21.8	21.8*	27.2	27.2†
Full time (over 30 hours)	37.7	37.7	13.4	13.4*	22.7	22.7†
Officially reduced working week (hrs per week)	16.8	12.4 (5.0)	11.3	12.9 (2.7)	7.6	10.9 (4.2)
Extra hours missed in the last week	12.0	14.0 (12.3)	7.2	13.6 (11.8)	3.0	25.0 (21.2)
Retired early due to MS	18.5	18.5	54.6	54.6*	36.4	36.4† ‡
Presenteeism (% of work performance affected)	25.4	18.1 (26.8)	16.4	30.5 (30.0)	16.7	27.2 (33.7)
Informal care						
Weekly hours of informal care received	56.1	10.7 (10.6)	83.5	15.5* (12.9)	80.3	15.2 † (11.7)

*Difference is statistically significant compared to the RRMS subgroup (p-value<0.05)

† Difference is statistically significant compared to the RRMS subgroup (p-value<0.05)

‡ Difference is statistically significant compared to the SPMS sub-group (p-value<0.05)

‡ Difference is statistically significant compared to the moderate sub-group of patients (p-value<0.05)

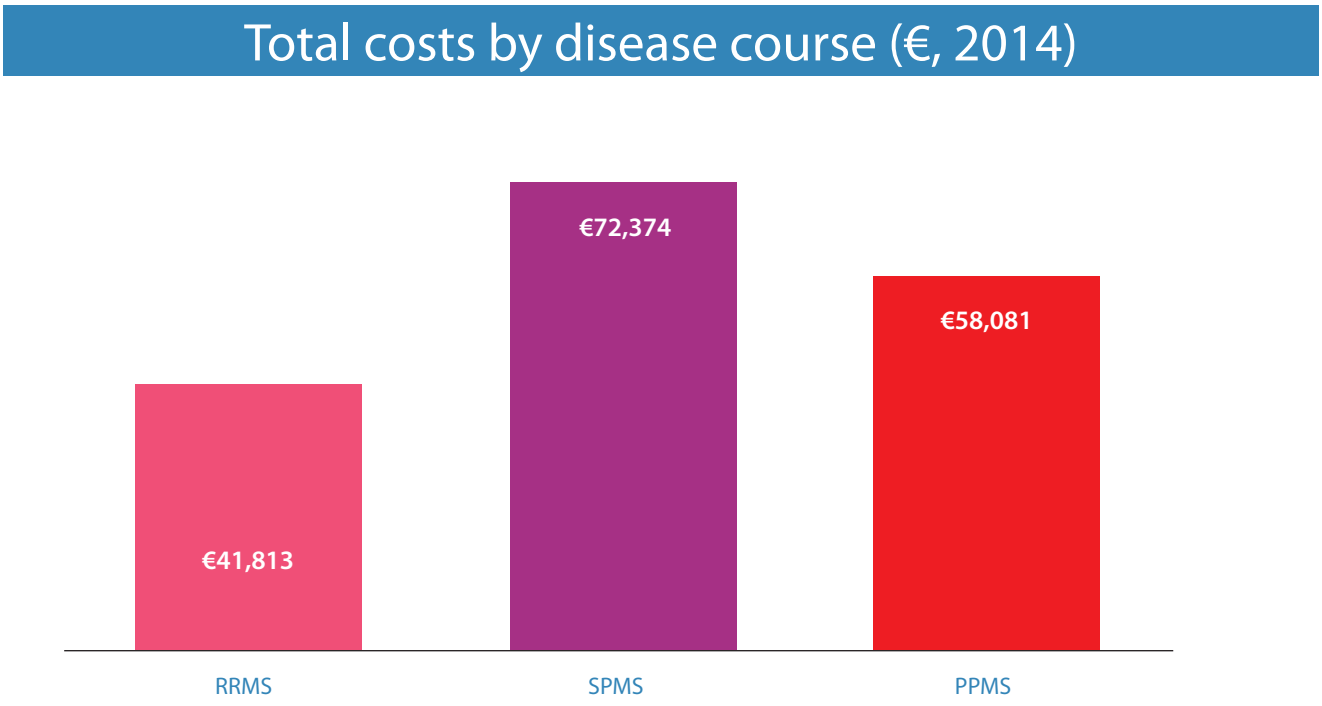
7.8.4 Costs by disease course (RRMS, SPMS and PPMS)

As in previous cost of MS studies, costs vary across the disease course spectrum. When looking at the component costs—within each group—indirect costs forms a larger share of total costs than direct costs. The relative contributions of the cost components however, differed among the subgroups; for example, indirect costs comprised a smaller proportion of total costs in RRMS compared to both SPMS and PPMS subgroups (47% for RRMS, 53% and 54% for those with SPMS and PPMS. While for those with RRMS, direct costs (37%) comprised a larger proportion than those in the SPMS (25%) or PPMS groups (21%). Intangible costs too varied across disease types, with intangible costs composing 16%, 22% and 24% for those with the relapsing-remitting, secondary-progressive and primary-progressive forms of MS, respectively.

Table 33. Costs by disease course (RRMS, SPMS and PPMS)

Disability level	Direct costs	Total indirect costs	Productivity costs	Informal care costs	Utilities EQ-5D	Intangible costs	Total costs (€,2014)
RRMS (n=374)	15,285	19,831	12,965	6,866	0.673	6,696	41,813
SPMS (n=97)	17,779	38,457	23,591	14,865	0.338	16,120	72,374
PPMS (n=66)	12,306	31,605	17,623	13,981	0.389	14,170	58,081

Figure 25. Breakdown of costs by disease course (RRMS, SPMS and PPMS)



8. Summary

8.1 Overall cost estimates for Ireland

The aim of this report was to estimate the economic burden of MS on those who have the condition and society as a whole, in Ireland. This study enriches the existing information base for MS in Ireland, and to that end describes how MS disability severity, disease type and MS relapses correlate with direct medical costs, informal care, productivity losses and intangible costs.

Our results show that MS imposes a significant economic burden on Irish society. In our study, we estimate that total costs attributable to MS as being €47,683 per person, per year. This estimate is in line with the conclusions in previous cost-of-illness studies of MS in Finland (Ruutiainen et al., 2015) and in France, Germany, Italy, Spain and the United Kingdom; with total costs ranging between €39,468 to €52,232 per person with MS (Karampampa et al., 2012a). Our estimate of €47,683 straddles the higher number reported in these studies, however, unlike in Karampampa et al., we endeavoured to estimate the intangible costs associated with having the condition, a cost which was estimated as being €9,038 per person and year. With respect to the existing Irish literature, our estimate for total costs attributable to MS is higher than that reported in Fogarty et al. (2014) (€38,226). This difference is primarily driven by the addition of intangible costs (€9,038) in our study and higher costs associated with informal care (€8,646 v €6,188).

Our results also highlight that as disability severity increases, so too does the economic burden. The total cost associated with moderate MS (€57,857) was 70% higher than our estimated cost for those with mild MS (€34,942); while the cost associated with severe MS was approximately three times the total cost for those with mild MS (€100,554). This finding echoes that of previous studies in the MS cost of illness literature, for example in Karampampa et al. (2012c) the total cost associated with moderate MS (€39,923) was almost double than their estimated total cost for people with mild MS (€21,174). While the total cost incurred by those with severe MS (€64,270) was about three times the total cost for people with mild MS. In Fogarty et al's Irish study, a similar pattern emerged, however the costs associated with severe MS was almost five times that of mild MS (€95,968 v €19,696), while the cost estimated representing moderate MS was over double that of mild MS. (€44,851 v €19,696). The ubiquity with which MS severity is a predictor of total costs in this study and in the international literature, highlights the importance of delaying disability progression from an economic perspective as well as it being a clinical priority.

8.1.1 Direct costs

We estimate the total direct costs per person in our study as being €14,895. In previous European studies in the MS medical space, informal care was categorised as a direct cost (Karampampa et al., 2012a, Kobelt et al., 2006b). Excluding informal care from the direct costs in these studies, our estimate falls within the range of those reported by Kobelt et al. (€13,966–€31,042 in nine European countries) and in Karampampa et al (€12,953–€24,835 in five European countries) (all costs inflated to

€ 2014). Our estimate is closer to the lower bound figures reported above, probably due to the fact that our respondents were recruited though MS Ireland, a patient organisation. In Karampampa et al. respondents were exclusively recruited from specialised clinics, while in Kobelt et al. 40% of the study respondents were clinic based. Our estimate also falls somewhat in line with that of Fogarty et al's Irish study. In this respect, Fogarty et al. estimated total direct costs at €17,968 compared to our estimate of €14,894. The disparity here is partly driven by the sample characteristics, as was the case in the European studies mentioned above, the previous Irish study was also clinic based. As a consequence, nearly twice as many respondents in their study reported having severe MS (12.7% v 6.6%). This is reflected in higher hospital/rehabilitation costs (€1,935 v €1,329) and considerably higher costs associated with professional help at home (€4,262 v €1,289).

As was the case with total costs, in our study, direct costs also increase as disability severity progresses from mild through to severe MS. Those with severe MS reported costs approaching double that of mild MS (€26,298 v €14,269), the direct costs associated with mild MS were slightly larger than those with moderate disability (€14,269 v €13,696). In Karampampa et al (2012c), direct costs for those with severe MS are just over double that of estimates for mild MS (€39,828 v €18,744), while the cost associated with moderate MS is 16% higher than that reported for mild subgroup (€17,287 v €20,216). In Fogarty et al (2014), the situation is a little different as the direct costs associated with severe MS, is by a factor of five larger than those with mild MS (€56,528 v €10,249) and more than four times that of moderate disability (€56,528 v €13,045). This large increase accrued to those with severe MS is primarily driven by the increase in costs associated with professional help at home, which escalate from €147 per person with mild MS to €26,231 with severe MS. The equivalent shift of costs in our study with respect to formal paid care is from €51 per person for those with mild MS to €10,249 per person with severe MS –once more highlighting the differences between the two sample populations with respect to disability severity.

8.1.2 Indirect costs

Similar to the majority of MS cost-of-illness studies (see Table 29): indirect costs outweighed direct costs in our study. Excluding intangible costs, indirect costs associated with MS in Ireland are estimated as being €23,750 and constitute 61.5% of total costs (excl. intangible costs). This is comprised of productivity losses of €15,056 and informal care costs of €8,646. Our estimate of €23,750 for indirect costs represents a 13.8% increase on the figure estimated by Fogarty et al. (2014), (€20,858). The variation is driven by higher informal care costs in our study (€8,646 vs €6,145), slightly higher productivity losses (€14,712 vs €15,056) and by the fact that we included an estimate for lost productivity at work due to MS, i.e., presenteeism (€1,668).

Table 34. Direct costs v indirect costs by country

Country	Author	Year	Direct costs	Indirect costs
UK	McCrone	2008	28%	72%
UK	Kobelt	2000	28%	72%
Ireland	Current study	2015	38%	62%
Norway	Svendsen	2006	39%	61%
Spain	Kobelt	2012	42%	56%
Netherlands	Kobelt	2006	42%	58%
Ireland	Fogarty	2014	45%	55%
Canada	Karampampa	2012	46%	64%
Germany	Kobelt	2006	47%	53%
Australia	Taylor	2007	57%	43%
France	Karampampa	2006	85%	15%

In our study and consistent with the international literature (Kobelt et al., 2006b, Karampampa et al., 2012a) the progression of disability severity was associated with increasing indirect costs. We found that indirect costs for those in the severe MS subgroup were three times higher than those with mild MS (€46,223 vs €15,470), while for those with moderate MS, the difference was almost double (€32,671 vs €15,470). A graded relationship between disability severity and indirect costs was also found in Fogarty et al. (2014), where indirect costs increased from €9,447 for those with mild MS to €31,806 and €39,440 for those with moderate and severe disability, respectively. At both ends of the disability severity spectrum, our analysis highlights higher indirect costs than the previous Irish study: informal care costs for those with mild MS were substantially higher (€4,697 v €820) and likewise for those with severe MS (€21,372 v €18,075). Furthermore, our estimates with respect to productivity losses were again higher for those with mild (€10,773 vs €8,627) and severe MS (€24,851 v €21,367). The divergence with respect to productivity losses is primarily driven by our inclusion of a presenteeism estimate, while the disparity in terms of informal care in the case of the severe subgroup, is possibly as a result of higher levels of severe MS in Fogarty et al's sample, and the apparent shift towards formal paid care and long term care institutions.

The economic costs associated with MS are considerable and are presented in this report from a societal perspective. It is however important to note, that the personal costs that people with MS face, on a day to day basis are significant and while not the main focus of this study, they constitute a considerable part of our overall costs (in terms of loss of earnings, travel costs, etc). An interesting and important focus for future research could be to specifically explore the personal costs that the MS imposes on those with the condition.

8.1.3 The cost of MS relapses

Supplementary to our approach to calculate the costs associated with MS in general, there was also a section in the survey which was specific to MS relapses. Information was garnered with respect direct and indirect health care use specific to the respondents' last relapse, therefore allowing the estimation of the costs associated with a single MS relapse (€2,438). In a similar way, O'Connell et al. (2014) estimated the *'Economic Costs Associated with an MS Relapse'* in an Irish context. The average cost per relapse in the previous Irish research was estimated at €3,571, some 46% higher than the estimate provided in the present study. The principal factor driving this disparity, is the proportion of those who required inpatient care as a result of their relapse. This was the case for 32% of the sample in the previous Irish research, while 18% reported requiring such care in the present study. This once more highlights the inherent differences regarding sample characteristics, between a clinic based study, such as O'Connell et al. (2014) and as is the case in the present study, where the study sample reflects those with less severe disability. Allied with this, the nature in which relapses are reported in this study, is likely to have had the effect of our sample being over-represented by those reporting having experienced mild relapses. This is so, as unlike in clinic based research, where relapses are confirmed by a neurology team, the relapses reported here, are done so on a self-report basis. While a global definition of a MS relapse[19] was provided to the study respondents, a person's definition of a relapse may not be the same as a medical definition. Indeed, just over half of those experiencing relapses, reported having them confirmed by a neurology team. Therefore, we cannot rule out that those in our study had difficulties in differentiating between mild MS symptoms and actual relapses. Being that as it may, our survey relies on people with MS recalling and self-reporting on their condition, therefore the personal insight and experience offered by the respondents, is given primacy in this report

Typically in the literature, the mean cost of a relapse is estimated by calculating the difference in costs between those who have the same level of disability (EDSS 5.0 or below), who had experienced a relapse (in a stated recall period) versus those who had not experienced a relapse (Ruutiainen et al., 2015, Kobelt et al., 2006b, Karampampa et al., 2012c). To be consistent with the previous research, we followed a similar approach and isolated our sample to those with the RR form of the disease with mild or moderate disability only (n=373) and calculated the difference in costs between those who did and those who did not report a relapse in the past year.

By doing so, we estimated that relapses were associated with an incremental annual total cost of €12,588 per person with RRMS, which was mostly attributable to indirect costs (€9,750) and to a lesser extent to direct resource use costs €2,838. By dividing the excess cost with the mean number of relapses (1.73) reported, the mean total cost per relapse was estimated at €7,261.

Following the methodology used in the previous research, the mean total cost per relapse is approaching 3 times higher than our estimate which assesses resource use based on the respondents last relapse (€7,261 vs €2,438). The larger estimate however, does not fully control for disability within the subgroup of those with RRMS. In our study and those reporting no relapses, 82% and 18% were in the mild and moderate disability subgroups, while for those in the relapse cohort, the proportion of those with moderate MS was much higher, at 34%. Therefore it is probable that estimating the excess cost attributable to relapses in this way, may be confounded by the varying levels of disability severity within the particular subgroups. Therefore we conclude that estimating the cost of MS relapses based on the resource use specific to the person last relapse, provides a more conservative and perhaps a more reliable estimate.

19. "The appearance of new symptoms related to your MS or very definite worsening of old symptoms, which lasted for at least 24 hours and occurred after you had been stable for at least a month and when you did not have a temperature, an infection or any other health trouble"

9. Discussion

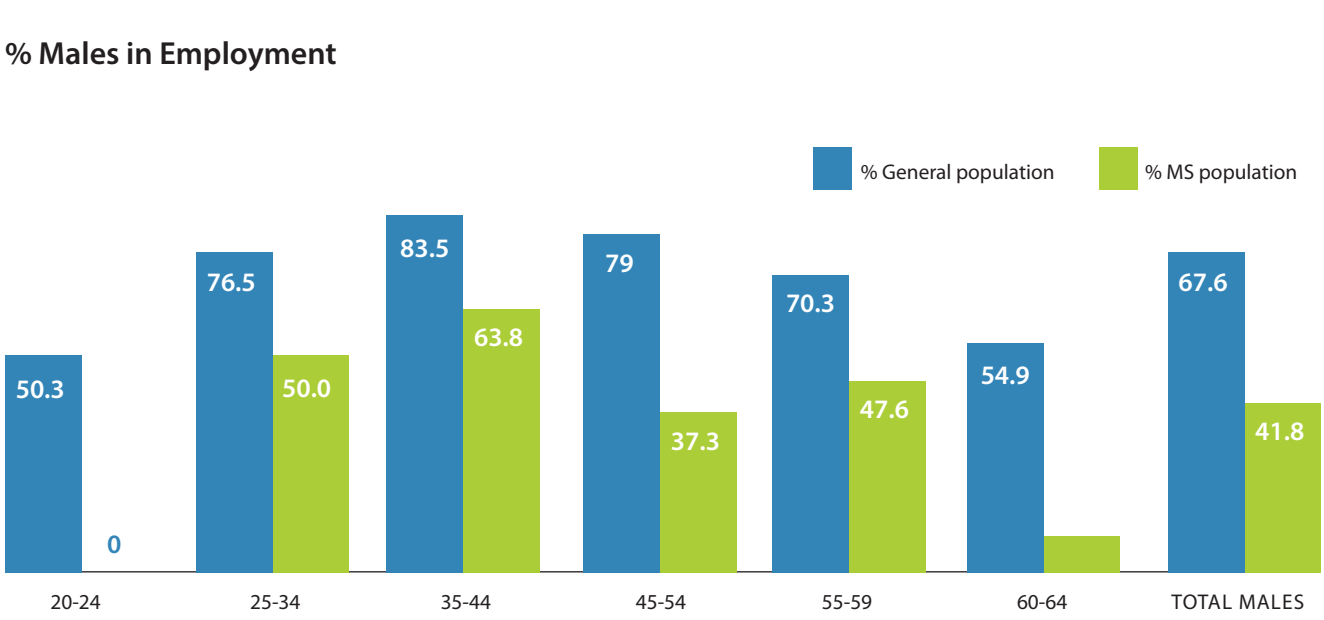
9.1.1. Employment

Productivity losses as a consequence of MS constitute 65% of our total indirect costs and are estimated at €15,056 per person. MS is associated with profound productivity losses for a variety of reasons. Since the average age of onset is between 20-40 years, MS impacts people at the prime of their working life. Furthermore, for those who experience relapses, or are unable to walk, or who experience extreme fatigue, it can be difficult to sustain a normal working life. This is apparent in our study where 26% of those in employment, felt it necessary to change jobs due to their condition, while close to 70% felt that the disease had limited their career potential.

Consequently, for those with MS, finding and remaining in employment can be a pervasive issue. This is illustrated by the employment rates evident in our study, where 41.7% of men and 43.2% of women report being in paid employment. These figures represent a 24% and a 38% decrease on the national averages for women (56.9%) and men (67.6%), respectively (CSO.2014). Low employment rates are also reported in the international literature: in the Kobelt (2006) European study, the proportion of those who worked ranged between 25-40%. While in the Fogarty et al (2014) Irish study, the corresponding figure was 40.1%.

As one would expect employment status varied by disability severity in our study (mild: 56.4%, moderate: 26%, severe: 15%) and disease type (RRMS: 51.0%, SPMS: 21.9%, PPMS: 27.2%). Furthermore, when we examine the employment rates by age in our sample, deep disparities are apparent between the MS population and the general population (see Fig 17 & Fig 18). As a case in point, the employment rates for men and women in our sample fall by 41.6% and 35.7%, respectively, when comparing the 35-44 and 45-54 age cohorts. In the general population, the corresponding fall in employment is markedly smaller, at 5.4% and 5.9%, for men and women, respectively. Advancing disability severity is precipitating this sizeable drop in employment. In our study the average age of those with mild disability was 43 while for those with moderate MS, the mean age was 51 –mean ages which fall into the age-groups examined above; this suggests a significant shift away from employment as people progress from mild to moderate MS.

Figure 26. Male population in Employment – General population vs MS population



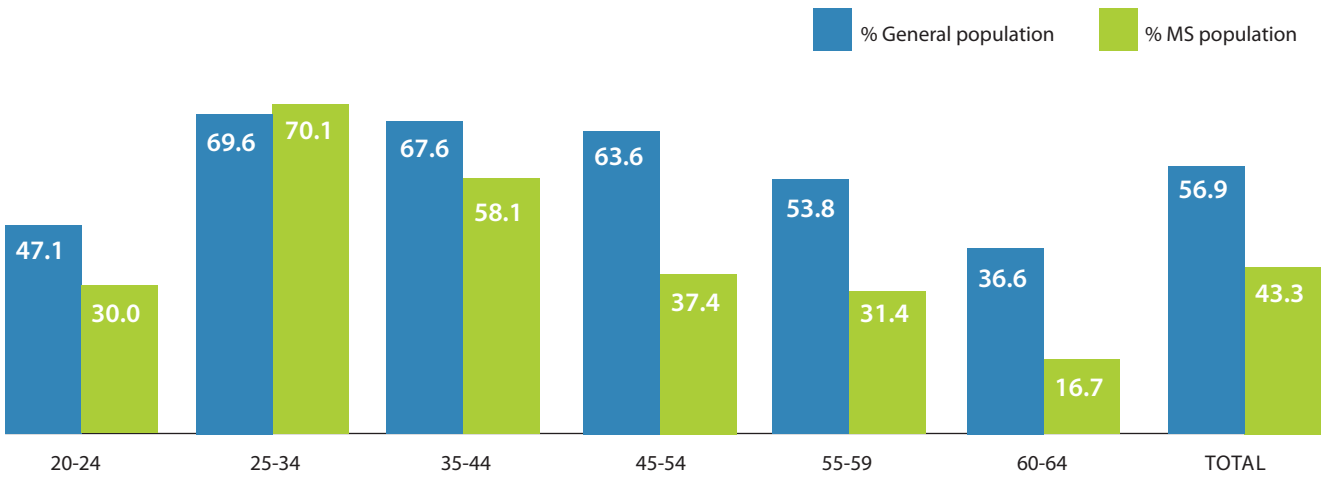
The principal factor driving the divergence in employment rates between those with MS in Ireland and the general population, is the necessity for many people to retire prematurely as a consequence of their MS. In our study, 34% of men and 25% women reported having to permanently withdraw from the workforce. The magnitude of this issue, emerges too in the international literature: for example, in Kobelt et al's European study, the proportion of those in early retirement because of MS ranged from 33% to 45%, while in the previous Irish study this figure was 36%.

For those who have their working lives cut short, the experience is likely to have a negative impact on income and income development. This is true for both men and women with the condition in Ireland. If we take the case of the 35-44 and 45-54 age groups in our sample, for men we see a 41.6% fall in employment rates (63.8% vs 37.3%), while in the general population when comparing the two age cohorts, those in the aged between 45-54 earn 12.4% more on average than those in the 35-44 category (€47,404 vs €42,173) (CSO, 2011). Similarly for women in our sample, those aged between 45-54 are 47% less likely to be employed compared to those in the 25-34 cohort, while average income increases by nearly 18%, for those in the general population when comparing the same age groups (€29,768 vs €25,251). This double-edged sword of rapidly decreasing employment rates at a time when average income typically increases, leaves many of those with MS at an impasse at a period in their lives when their peers are at their most productive.

While finding and remaining in employment can be a pervasive problem for those with MS, it is also the case that the presence of symptoms related to MS, can inhibit people with the condition while at work and consequently impact on productivity. There is mounting evidence that presenteeism, (i.e., reduced productivity while working) —may be a significant factor when evaluating work productivity losses in individuals with chronic diseases. As a case in point, a study examining the impact that arthritis has on work productivity estimated that presenteeism accounts for 41% of total productivity losses, while absenteeism constitutes a mere 10% (Li et al., 2006).

In the present study, 17% of the total productivity losses were due to presenteeism while half that figure was attributable to absenteeism (8.5%) and in total, for those in paid employment (n=254), the average percent of work performance affected by MS symptoms was 18.9%.

Figure 27. Female population in Employment – General population vs MS population



The literature regarding the impact of multiple sclerosis on presenteeism is relatively sparse; the two studies that did so however, both reported lower estimates for work performance affected by MS, than the 18.9% estimate presented in this study. In Tauhid et al. (2015), the corresponding figure is 13.5%, while in Glanz et al. (2012), the figure was lower still at 11.9%. The disparity here is probably due to the differences in study sample characteristics: the former study's cohort was dominated by mildly affected people with RRMS, while in the latter, the sample was drawn from those with CIS or RRMS with mild disability. When we isolate our sample to just those with RRMS and mild disability our estimate of 15.3% while still higher, comes closer to those in the previous studies.

Productivity losses were measured in this study using the human capital (HC) approach. This approach assumes that the value to society of productivity loss should be measured as the present value of lost time according to the market wage. In the absence of any detailed information about the human capital, experience, skills etc. of people with MS in our sample, productivity losses associated with reductions in working hours or sick leave and both presenteeism and permanent withdrawal from the work force, due to MS, were based on national gender-stratified average gross hourly and annual earnings, respectively. This was the approach followed in the previous the Irish research on the cost of MS (Fogarty et al., 2014) and so too in the international literature (Kobelt et al., 2006b, Karampampa et al., 2012a)

It is argued however, that the HC approach may overestimate the costs of foregone productivity. This is so, as short-term, illness-related work absences may partly be compensated by colleagues during normal working hours, while illness-related, permanent withdrawal from the workforce, can be compensated by employing someone who was previously unemployed (Smith et al., 2011). However, it has also been argued that common productivity cost estimates are, indeed, underestimations of the actual costs involved, since no compensatory allowances are made for the impact of absenteeism and presenteeism on co-workers' productivity, in the context of team-dependant production. Where at most, an entire team's productive output may be at risk when one of its members experiences health problems (Krol, 2012) Being that as it may, an alternative to the HC approach: the frictional cost (FC) method, has been suggested to assess productivity losses owed to ill-health (Berger et al., 2001). The frictional cost approach, only counts those hours until another employee takes over the absentee's work and it assumed that long-term absentees are replaced within this "friction period" (Krol, 2012). A recent Irish study, utilised a friction period of 9.9 to 13.3 weeks, to estimate productivity losses associated with head and neck cancer (HNC) in Ireland (Pearce et al., 2015). Using the mid-point of this friction period (11.6 weeks), we provide a supplementary estimate to that provided using the HC approach (€15,863) and therefore estimate the productivity losses attributable to MS using the FC approach as being €3,833 per person.

This research serves to highlight the considerable work-life challenges associated with having MS in Ireland and the substantial productivity losses associated with such challenges. Particularly striking in this respect is the significant proportion of our study sample that felt it necessary to permanently withdraw from the workforce as a consequence of their condition. While legislation and changes in attitudes mean that workplaces are becoming more disability friendly (MS Ireland) – our findings demonstrate that more could be done to improve employment opportunities and to foster flexible work practices, that may help to enhance the work-life prospects of those living with MS in Ireland. In this regard, the Multiple Sclerosis International Federation's (MSIF) survey of 8,681 people with MS, 5 key factors emerged that according to the respondents, would help keep people with MS in the workplace (Chandraratna, 2010).

1. Stable disease assisted by effective treatment.
2. Supportive employers and colleagues.
3. Seated work
4. Flexible work hours
5. Computer adjustments

9.1.2 Informal care

Disease progression in multiple sclerosis leads to dramatic changes in a person's ability to perform daily activities and consequently, increases reliance on external help. For many, this external help manifests in the form of unpaid, informal care from family and friends. In our study, 63% of our sample reported receiving on average, 12 hours of informal care in the previous week.

While this informal care is provided free of charge, it is often not without cost. The caregiving responsibilities that are associated with MS, impacts on the lives of those involved in the caregiving process (Parise et al., 2013). This is apparent in our study, where 33% report that their MS impinges on their children being able to partake in normal childhood activities, while 73% report that it is likely that their children worry excessively about their parent's health.

Informal caregiving for those with MS has received considerable attention in the international literature. In the Kobelt et al (2006) study in nine European countries, estimates vary from 47.5 to 62.2% receiving informal care and hours of care varied from 9.5 to 32 hours per week. In Fogarty et al's (2014) Irish study, the proportion of those requiring informal care were markedly different, with just

21.5% in receipt of informal care (21.4 hrs per week). This is probably due to the degree to which their sample was affected by severe MS and the apparent substitution away from informal care to formal paid care and care in long-stay institutions.

In our study, informal care costs amounted to €8,648 per person and comprised 35% of our total indirect costs and constituted 22% of our total costs (excl. intangible costs). The costs attributable to informal care varied by disability severity (Mild MS: €4,697, Moderate: €12,583, Severe: €21,372) and by course of illness (RRMS: €6,866, SPMS: €14,865, PPMS: €13,981). This variation by severity and disease course is also reflected in the literature (Kobelt et al., 2006b, Karampampa et al., 2012a, Fogarty et al., 2014). Informal care costs for those with mild MS were however, considerably higher in our study compared with that reported in Fogarty et al (2014), (€4,697 vs €820) and in Karampampa et al. (2012a) (€4,697 vs €830). This may be due, in part, to differing methodologies used to classify disability severity. In this study, the level of disability severity was self-reported, whereas in both Fogarty et al (2014) and Karampampa et al. (2012a), respondents were assessed by clinicians and categorised based on EDSS scores – perhaps intimating higher levels of disability severity in our mild subgroup and/or the inclination for respondents to self-report mild disability.

Using a similar approach as Fogarty et al. caregiving was valued at the wage the caregiver would earn if in paid employment, based on national mean annual earnings. Therefore, we did not distinguish between carers who were in paid employment and those who were not. This approach may potentially lead to an overestimation of the actual productivity losses to society. However, once more in line with the approach in Fogarty et al. (2014), we applied a cap on caregiving time in line with a 40 hour week, ensuring a more conservative estimate. Removing this cap results in average caregiving hours of 15.3 per week resulting in an annual cost of €11,101 per person. A further, more conservative method, when valuing caregiving time, is to do so at the national minimum wage (€8.65 per hour) (O'Shea and Kennelly, 2008). Following such an approach results in an annual cost attributable to informal care, in our study, of €4,321 per person with MS.

9.1.3 Utility and intangible costs

While multiple sclerosis is associated with a significant cost burden, the condition also impinges significantly on the quality of life of those with the condition. We assessed quality of life in this study by applying the commonly used validated survey instrument EQ5D-5L to estimate the utility, or health related quality of life (HrQol) of people living with MS.

The mean utility for the sample derived by from the EQ-5D was 0.59. A figure, which when compared to the UK population norm of 0.86, represents almost a 32% decrease in self-reported QoL (Kind et al., 1999). There was a graded relationship between severity of disease and utility value, those with mild, moderate and severe disability reporting mean values of 0.718, 0.492 and -0.027 respectively. Differences were also apparent with respect to disease course, those with the RR form of the disease reporting significantly higher mean index values (0.67) than SPMS (0.34) and PPMS (0.39) ($p<0.001$). Differences also emerged when restricting our sample to those with RRMS, with those experiencing a relapse reporting lower utility values (0.64), than those in the no relapse cohort (0.70) ($p<.02$).

The utility values estimated in our study are consistent with that estimated in the international literature (Kobelt et al., 2006b, Karampampa et al., 2012a) and also in previous Irish research (Fogarty et al., 2013). Indeed, the mean utility value of 0.59 estimated here is analogous to that reported in Fogarty et al., (2013). Consistency in this respect was expected, as previous studies in the area have demonstrated that even when comparing utilities across as many as nine European countries, utility values were almost identical (Kobelt et al., 2006b).

Differences, however, did exist between our results and those reported elsewhere. In Fogarty et al (2014), no significant differences emerged between men and women in their sample. Whereas we found a sizeable difference with scores of 0.619 and 0.507 for women and men, respectively ($p < 0.01$). *This may be explained, as in multiple sclerosis, onset of symptoms in women appears to be earlier than in men, but men tend to exhibit a more progressive and severe disability course (Whitacre et al., 1999)*. This is reflected in our sample demographics with men constituting 22.5% of our mild MS cohort, while the proportion of men in the moderate and severe cohorts were 35.6% and 43.9%, respectively.

Differences were also apparent with respect to the most severe health states. In Kobelt et al (2006b), this was so, as the utilities measured using the EQ-5D-3L were truncated at zero, ruling out health states worse than death (WTD). In Fogarty et al (2014), the mean utility valuation for the worst health state was –0.22, while in our analysis, we report a figure of -0.03. This difference is largely due to sample characteristics and the fact that in the previous Irish study, the sample was clinic based and were more affected by severe MS. This is reflected in a larger proportion of those reporting health states WTD in Fogarty et al study (9.9% v 6.6%).

9.1.3.1 Intangible costs

Extending the EQ-5D analysis to include a monetary estimate for the clearly diminished HrQol associated with multiple sclerosis allowed us to present an estimate for the intangible costs associated with the condition. While typically not included in cost-of-illness studies, applying monetary values to such intangibles as self-care, pain, mobility, and anxiety or depression, offers a vehicle to highlight the tremendous hidden costs associated with having a long-term, progressive, chronic condition such as multiple sclerosis. Furthermore, intangible costs have been included in previous studies of the cost of MS, (Henriksson et al., 2001, Kobelt et al., 2006b) and by including same, we can offer intangible cost estimates that can be compared to those reported previous studies.

In our study, by calculating the difference in utilities between our sample and an age and sex-matched sample of the general population in the UK (Kind et al., 1999), the utility loss due to MS translated into a mean QALY loss of 0.28. Using the same methodology, a remarkably similar mean QALY loss of 0.27 was reported in Kobelt et al (2006c). While in Henriksson et al (2001), due to lower mean QALY estimates, this value was smaller (0.185). In Kobelt et al, the authors apply a threshold value of €50,000 to their QALY loss estimates and also apply a figure three times gross domestic product (GDP) per capita. Following the latter approach would imply a threshold value of €119,619 for Ireland and a resulting intangible cost estimate of €32,297. Following a more conservative approach, we use threshold values of €20,000 and €45,000, in which the willingness-to-pay for a unit of effect (life year or QALY) in Ireland, is expected to lie. Using these values for a QALY lost, intangible costs for MS in Ireland are calculated as being in the range of €5,562 to €12,515 per person and year.

9.1.4 Depression & anxiety

Coping with major challenges, such as the direct effects of multiple sclerosis on limbic system structures and the negative effects of functional impairment on life satisfaction and self-esteem, can place many of those with multiple sclerosis under huge psychological pressure (Chwastiak et al., 2014). This pressure for many, may manifest in terms of an increased risk for depression and/or anxiety. Indeed, prevalence estimates for depression and anxiety are typically much higher in MS populations compared to the general population and also with respect to other chronic medical illnesses (Schubert and Foliart, 1993, Schiffer and Babigian, 1984). Lifetime prevalence estimates for depression range from 23 to 54%, while point prevalence estimates range from 27 to 54% (Chwastiak et al., 2014). A similar pattern emerges in the literature with respect to anxiety, where the prevalence of reported anxiety amongst people with MS has varied from 14% to 41% (Korostil and Feinstein, 2007, Janssens et al., 2003). In our study, 33% of the sample reported having received a diagnosis or had been treated for depression since being diagnosed with MS, while the corresponding figure was 27% for anxiety. This signifies the tremendous psychological impact associated with having multiple sclerosis, as estimates for the prevalence of depression and/or anxiety in the Irish general population are reported to being close to 10% (Doherty et al., 2007).

In our study, we also explored the relationship between MS severity and the presence of depression and/or anxiety. There is debate in the literature to whether disability severity in the form of increased functional disability is associated with increased rates of depression – some studies suggest that those with more advanced disease are more likely to experience depression (Surridge, 1969, McIvor et al., 1984). While others report that the frequency or severity of depressive episodes among people with MS is independent of the severity of multiple sclerosis (RABINS et al., 1986). In the present study, we found a graded but non-significant relationship between disability severity and having a depression diagnosis, further adding to the ambiguity currently present in the research. Similarly, we find no significant differences with respect to course of illness (relapsing-remitting, primary progressive, or secondary progressive) and depression, this result is commonly reported in the literature (Chwastiak et al., 2014, Beiske et al., 2008, Koch et al., 2008). These findings suggests that even though disability increases as the disease progresses, people with MS, as is the case with other chronic illnesses, may adapt to their condition over time and develop coping strategies to deal with the psychological burden.

While no significant differences emerged with respect to severity or course of MS and a depression diagnosis, differences were apparent with respect to anxiety. Those with severe MS were almost twice as likely to have received a diagnosis or been treated for anxiety (24.7% vs 47.4%, $p<0.001$) compared with those with mild disability. While those with SPMS were 45% more likely to have diagnosis compared with those with the RR form of MS ($p<0.05$). Those with SPMS were also more likely than those with PPMS to have an anxiety diagnosis with a mean difference of nearly 18% ($p<0.05$). Although previous studies suggests a moderate association between disability severity and anxiety (Beiske et al., 2008), our results need to be treated with caution in this respect as in our survey, the respondents were asked about being treated or diagnosed with anxiety since the onset of MS. In our sample, those with severe MS and those with SPMS reported longer periods since the onset of MS, in comparison to those with mild, or moderate MS and in the case of SPMS to those with RRMS or PPMS. Therefore it is likely that the higher estimates for anxiety diagnoses in the severe and SPMS cohorts are influenced by the longer period of time the respondents had to receive such a diagnosis.

The strongest predictor of a diagnosis of depression and anxiety in our sample was whether the person had experienced a relapse in the past year. Those who reported having a relapse were 47% and 41% more likely to report a depression ($p<0.001$) or anxiety

($p<0.05$) diagnosis respectively. In this cohort, no significant differences emerged with respect to disability severity and time since onset, intimating that those who experienced a relapse in the past year may have their mental health diminished as a consequence. This conclusion was also reached in Di Legge et al. (2003), where the authors evaluated anxiety, depression in a sample of people with clinically isolated MS and found that over 3-years, depression was higher in those experiencing relapses than in those who remained relapse-free. It is possible however, that the reverse may be true and that people displaying depressive symptoms may be more likely to report a relapse because an altered appreciation of certain symptoms.

As discussed above, the prevalence of psychological comorbidities such as depression and anxiety are extremely common for those with MS, so much so that prevalence rates may be somewhere between three to four times higher than those found in the general population (Patten et al., 2003, McGuigan and Hutchinson, 2006). As a consequence, there is also a societal cost associated with the excess numbers of those with depression and anxiety in the MS population. Assuming a total prevalence figure of 8,000 people in Ireland with MS, we estimated this cost as being € 398,963 per year. This figure represents medication costs and extra GP visits that are associated with depression and anxiety. While this figure does not include other direct costs such as hospitalisations and indirect costs such as additional productivity losses and informal care costs due to depression and/or anxiety, it still represents a sizable sum and serves to highlight the extent of the psychological burden and the societal costs associated with psychological comorbidities which are commonplace for those with multiple sclerosis in Ireland.

9.2 Does reducing relapses save resources?

Relapsing-remitting MS (RR-MS) is the most common form of MS, with approximately 80-85% of all people with MS experiencing a relapsing–remitting (RR) onset of the disease, with 65% of those, in time, entering the secondary progressive (SP) phase (Balk et al., 2014). It is estimated that those with the RR form of the disease represent approximately 50% of all those with the condition in Ireland (McGuigan et al., 2004, McDonnell and Hawkins, 1998).

RRMS is characterised by unpredictable acute attacks (known as relapses) accompanied by worsening of symptoms or the appearance of new symptoms, followed by periods of remission during which there may be a full or partial recovery from the trauma of the relapse. Relapses can last for days, weeks, or months, and can be physically debilitating to varying degrees, causing distress to the person experiencing the relapse and also to their family and caregivers (Raimundo et al., 2013). Furthermore, relapse activity is correlated with long-term disability progression, with increased number of relapses early in the course of the disease associated with a greater risk of EDSS deteriorating over the life-course of the person with the condition (Sormani et al., 2010).

While it is manifest that relapses place significant physical and psychological costs on the person with MS and their family, research also points to increased use of inpatient and outpatient resources, GP services and medication use (Raimundo et al., 2013, O'Brien et al., 2003). For example, in Raimundo and colleagues (2013), the authors report that the direct annual cost (non-DMT) MS was €11,904 higher, representing nearly an 82% increase in costs for those who experienced two or more relapses. While in O'Brien and colleagues (2003), low, medium and high level relapses were all associated with increased resource use and cost, with inpatient care proving the most costly; their results suggest that that the cost of managing a relapse typically increases more than six fold if inpatient care is involved in managing relapses. A result which was echoed in a recent Irish study, where O'Connell and colleagues find that higher direct costs were driven primarily by hospital admission and length of stay (O'Connell et al., 2014). It appears that relapses that are symptomatic of RRMS incur significant costs on the person with MS and on healthcare system.

The increased direct healthcare costs reported elsewhere are also reflected in our sample; the mean total direct costs for those who reported no relapse (n=347) in the past year were lower than those who reported at least one relapse (n=247) and lower still than those who reported two or more (n=126). These differences were primarily driven by higher total mean costs for hospitalisations, MRIs and GP visits. In our survey we also asked about the resource use specific to our respondents' last relapse, enabling us to estimate the costs associated with a single relapse. As a consequence of their last relapse, 37% had received an MRI, while 46% and 18% had visited a GP and were admitted to hospital, respectively (see Table 27.) These results point to the considerable direct costs associated with managing MS relapses.

It is also the case that increasing indirect costs are associated with the frequency and severity of multiple sclerosis relapses. In O'Connell et al. (2014), the authors report indirect costs *(loss of earnings, partner's loss of earnings, childcare, meals and travel costs)* increased from €104 for a "low intensity relapse" to €438 for a "moderate intensity relapse" and escalated to €3491 for a "high intensity relapse," where loss of earnings was the main cost driver, representing 85% of total indirect costs. So too Parise et al. (2013), where the authors estimated indirect costs associated with a relapse by analysing a sample of people with MS, categorised into cohorts of no, low/moderate, and high severity relapse. The authors reported incremental costs (compared to the no relapse cohort) of €1,412 and €2,679, for low/moderate, and high severity relapses respectively. Once more absenteeism and this case also disability payments formed the bulk of the indirect costs. Interestingly, in Parise et al. (2013) the authors also investigated the impact of relapses on those providing care to those experiencing relapses, finding that more frequent relapses versus no relapse translated into a significantly

greater cost burden for caregivers. In a similar manner to the studies discussed above (O'Connell et al., 2014, Parise et al., 2013) we both compared the indirect costs associated for those who had a relapse in the last year and those that did not, and also the indirect costs associated with our respondents' last relapse. Doing so, highlights that the frequency and severity of relapses is associated with considerable increases in indirect costs

As discussed above, the processes involved in treating relapses incur large direct and indeed large indirect costs. Prior to the advent of Disease-modifying therapies (DMTs), the primary disease management strategy for people with RRMS, involved simply managing these acute attacks (relapses) when they occurred; since then however, the medical landscape has changed dramatically. In 1993, the FDA approved the first DMT for RRMS, subcutaneous (SC) interferon (IFN) IFN-b-1b, and this was quickly followed by intramuscular interferon (IFN) beta-1a, SC IFN beta-1a, SC glatiramer acetate (GA) teriflunomide and dimethyl fumerate. These first-line treatment for RRMS remain the foundation of many MS treatment algorithms. Second-line treatments for RRMS include the oral DMT for RRMS fingolomoid, SC alemtuzumab and natalizumab which is intravenously administered (monthly)

DMTs have revolutionised the treatment of RRMS, as rather than just managing symptoms, these therapies actively reduce relapses, reduce magnetic resonance imaging (MRI) measures of disease activity and delay disability progression (Weinstock-Guttman, 2013) .

Both first- and second-line DMTs have been shown to be effective in the treatment of RRMS, however, to varying degrees. For example, IFN betas have been associated with an approximate 30% reduction in the annualized relapse rate compared with placebo, as well as significant decreases in MRI markers of disease activity compared with placebo. Similar results have been reported for GA, with no significant differences in relapse outcomes or disease progression observed in direct comparative studies of GA and SC IFN beta-1b or IFN beta-1a (Weinstock-Guttman, 2013). Dimethyl fumerate has also been shown to be effective in the treatment of RRMS, displaying significant decreases in relapse rates and reductions in disability progression compared with placebo.

Second-line DMTs display increased efficacy compared to their predecessors and may improve individual adherence due to less frequent administration or due to the convenience of oral administration. For example, in a 2-year study, the oral DMT fingolimod, reduced annualised relapse rates by 54% to 60%; furthermore, disability progression was significantly reduced compared with those receiving placebo (hazard ratios, 0.68-0.70) (Kappos et al., 2010). While natalizumab, reduced the frequency of relapse by 68% and disability progression sustained over 12 weeks by 42%, in a 2-year study (Havrdova et al., 2010). Also in a 2-year study, Alemtuzumab which is administered yearly by IV, was associated with significant reductions in the relapse rate, disability progression, disability scores, and MRI measures of disease activity compared with SC IFN beta-1a (Weinstock-Guttman, 2013). Second-line DMTs offer increased efficacy, however, they currently lack the longer-term safety profile of the older injectable first-line therapies. As further safety data for these therapies become available, it is expected that their role in the treatment of MS will become even more firmly established, potentially improving disease status and quality of life for those with the condition (Weinstock-Guttman, 2013).

The cost of DMTs are however, not insignificant. In Ireland, annual first-line treatment costs €15,000 while escalated second-line treatment has an average cost of €22,000 (O'Connell et al., 2014). This expense is often considered in the context of other health service costs averted (e.g., reduced hospitalisations) yet the effectiveness of DMTs, via the reduction of relapses, has also had a significant impact on the QoL and independence of people with MS which, as we have demonstrated, represents a significant societal cost saving. As a case in point, in our sample 37.8% of those experiencing at least one relapse in the past year were in paid employment, while for those with no relapse this figure was 46.4%, a proportional increase of nearly 23% ($p<0.05$). The gap widens further when we include those who have had two or more relapses, where the increase apparent is 44% ($p<0.05$). While the physical effects of relapses may play a major role in the choice or the ability to take up or continue employment, having active MS may also have negative consequence in terms of mental health, which in turn may also play a role in the reduced employment rates. To illustrate the point, in our sample those with at least one relapse were 47% and 41% more likely to have a depression ($p<0.001$) or anxiety diagnosis ($p<0.05$), respectively. Taking it a step further and dichotomising our cohort into those with no relapse in the past year, who were in paid employment and those with a relapse but were not employed, the disparities with respect to the diagnosis of a mental health problem became even starker. In this case, those in the relapse group were 3.7 times and 2.6 times more likely to have a depression ($p<0.001$) and anxiety diagnosis ($p<0.001$), compared with those not in employment. This study is cross-sectional in nature and therefore we cannot determine the direction of these associations, however, it is reasonable to suggest that there is a complex multi-directional process inherent in the relationship between active MS, employment and mental health problems.

As already discussed, relapses are associated with significantly increased direct costs, such as hospitals, GP visits and increased medication use, while also being associated with considerable increases in indirect costs, such as absenteeism and escalated caring costs –and as we have demonstrated, those with active MS display considerably higher levels of depression and/or anxiety compared with the general population, which may further act to increase the societal cost associated with MS relapses. It is therefore reasonable to suggest that reducing relapse rates via DMTs will have the effect of reducing these costs. Indeed, in Birnbaum et al (2009), the authors report substantial significant reduced annual direct and indirect costs for those being treated with DMTs compared to those untreated.

Furthermore, the costs attributed to MS are highly dependant on the level of physical disability experienced by the persons with the condition. Numerous studies examine the graded relationship that exists between level of disability due to MS and healthcare

resource consumption and indirect costs (Kobelt et al., 2006b, O'Connell et al., 2014, Karampampa et al., 2012a, Karampampa et al., 2012b). For example, in Karampampa et al (2012) mild disability (EDSS score 0-3) was associated with annual costs of €22,045, while moderate (EDSS 4-6.5) and severe disability (EDSS score 7-9) was associated with costs of €34,226 and €57,268, respectively. These findings were also reflected in our study, with annual costs of those with mild, moderate and severe MS estimated as being €34,942, €57,857 and €100,554, respectively.

As is the case with the reduction of annualised relapse rates (ARR), the use of DMTs in treating MS can also reduce the economic burden of the condition by delaying disease progression. Several high-efficacy immune therapies can reduce the risk of disability progression in RRMS. Trials of fingolimod, natalizumab and subcutaneous IFN beta-1b treating people with RRMS have demonstrated significant reductions in the risk of 6-month confirmed disability progression, with effect sizes being in the range 40–60% (Wiendl and Meuth, 2015).

Due to relatively short timeframe within which DMTs have been used to treat MS, definitive evidence with respect to the effect of DMTs on long-term disability, remains lacking (Kister et al., 2012) . There is however, mounting evidence to suggest that the accumulation of disability as a consequence of MS, has indeed been stalled. As a case in point, Kister et al (2015), using *MSBase Registry* data from 20 countries (n=11,108) report that during the 1996–2010 period, enrollment age for peoples with EDSS 4/4.5 increased by 7.9 years, from 43 to 51 years ($p<0.001$), and for EDSS 6/6.5 — by 4.9 years, from 48 to 53 years ($p<0.001$) (Kister et al., 2012). While in a population-based registry in Nova Scotia, Canada, the median time to reach EDSS 6 increased by approximately 4 years following the introduction of DMTs (Veugelers et al., 2009). Furthermore, the results from a population-based study from Gothenberg, Sweden suggest that since the introduction of DMTs, the onset to the progressive phase of the disease has been delayed by 7–9 years (Tedeholm et al., 2006). Allied with this is the mortality advantage found in Goodin et al. (2012), where after a median of 21.1 years from RCT enrollment, those originally randomly assigned IFNβ-1b 250 µg showed a significant reduction in all-cause mortality over the 21-year period compared with placebo ($p = 0.0173$).

While there are other potential explanations for the apparent improvement in outcomes for those being treated with DMTs, such as changes in environmental exposures and health behaviors (e.g. decreasing smoking rate), and improvements in the recognition and management of symptoms and complications of MS; it seems likely that the role played by DMTs in delaying the long-term progression to disability is considerable (Kister et al., 2012).

Those in the sample who experienced relapses in the past year, utilise more resources than those who were relapse free, and those experiencing two or more relapses – even more so. As an extension of this, it is therefore reasonable to suggest that by reducing relapse rates, resources will indeed be saved. The resources in question are not simply direct in nature, such as hospitalisations and GP services, but also manifest in terms permanent withdrawal from the workforce, absenteeism and increased caring costs. Related to this, we have demonstrated that those with active MS, display much higher levels of depression and/or anxiety compared with the general public, it is likely that this will also have associated costs, both direct and indirect. Furthermore, but outside the scope of this study, the increased caregiving responsibilities that are associated with MS relapses, can place both a financial and psychological burden on those who are involved in the caregiving process (Parise et al., 2013).

9.2.1 Estimated savings associated with reducing relapse rates and delaying disability progression

One of the key drivers in the overall societal cost of MS, is the progressive disability people experience as they move through the disease course. Targeted treatments such as Disease modifying therapies (DMTs), although not without cost, actively reduce relapses, MRI disease activity and furthermore are likely to play a role in delaying long term disability progression, which proves so burdensome as the disease course progresses.

First-line DMTs have been shown to reduce annual relapse rates by 30% compared with placebo, while newer second-line therapies by up to 60% (Weinstock-Guttman, 2013). In this study, we estimate the total annual societal cost attributable to MS relapse as being €16.9 million. Applying the 30% to 60% range mentioned above, to our estimate for total cost of MS relapse, (as reducing relapses by 30% to 60% will also have the effect of reducing the cost of relapses by the same figure), suggests the potential to reduce overall costs associated with MS, in the range of €5.1 million to €10.1 million annually.

There may be also potential cost savings associated with delaying disability progression. In an attempt to provide a guide to what such cost savings may look like, we assumed a linear relationship between EDSS scores and our societal estimates of mild (€34,942), moderate (€57,857) and severe MS (€100,554). In so doing, we estimate the cost associated with a one point increase in EDSS score as being €10,952. Furthermore, we assume that DMTs will reduce disease progression by 20%-40% (Wiendl and Meuth, 2015). Applying this range of the associated reduction in disability progression, to our estimate for a one point increase in EDSS score, results in estimated cost saving of €2,190 to €4,380, per person with RRMS. When extrapolated out to the broader population of people with MS in Ireland (9,000) and assuming that 50% of those have the RR form of the disease, provides for a range of potential annual savings from €9.8 to €19.7 million. In conclusion, reducing relapse rates and delaying disability progression may be associated with estimated savings in the region of €15-30 million, per annum.

10. Limitations

While we have been rigorous in attempting to place a monetary value on the various costs associated in multiple sclerosis in Ireland; this study had a number of limitations.

Firstly, and similar to all cost-of-illness studies which utilise self-report data: our cost estimates are only as reliable as the resource utilisation data upon which they are based. All resource use data were based on that self-reported by our study respondents, using an online questionnaire (n=574) and a postal questionnaire (n=20). Self-report data may be open to recall bias. For example, it has been recognised that respondents tend to under-report their hospitalisations for longer recall periods and overstate for shorter (Bhandari and Wagner, 2006). Being that as it may, there is evidence that self-reported resource utilisation data, is as reliable as other sources, including administrative records (Snell et al., 2013). Furthermore, the instrument used to assess resource use in this study is commonly applied in cost-of-illness studies and its reliability and validity has been previously established (Beecham and Knapp, 2001)

Secondly and pertaining to our study sample: due to the rigour of completing such a comprehensive survey, it is probable that our study sample is over represented by those with mild disability, this may have the effect of limiting the numbers who are bed-bound or live in residential care. Such a limitation may have the effect of underestimating costs with respect to the consumption of certain resources. These include hospitalisations, care provided in long-term care institutions and care provided in the home, both formal and informal. While this may be so, unlike clinic based studies, the geographical dispersion of our study sample, closely resembles that of the general population of Ireland (see figure in appendix), ensuring a broadly representative sample.

Thirdly, while a global definition of an MS relapse was provided to the respondents in the survey; unexpectedly, relapses were reported across all levels of disability and disease types. Therefore, we cannot rule out that those in our study had difficulties in differentiating between disease progression and relapses. This may have the effect of over-estimating the average annual relapse rate reported and consequently, lead to an overestimation of the annual costs attributable to MS relapse in Ireland.

An additional limitation is the lack of detail regarding medication use for the study sample. To reduce the burden on the survey respondents, detailed information regarding current medication use was not requested as part of this study– as the societal cost of these can be imputed using alternative sources. To that end, average medication costs were attained from previous Irish research in the cost of MS area: namely: Fogarty et al. (2014) and adjusted to reflect the levels disability severity in our sample.

11. Conclusions

This report highlights the economic consequence of that multiple sclerosis for those who have the condition and society as a whole in Ireland. This study enriches the existing information base for MS in Ireland, and to that end describes how MS disability severity, disease type and MS relapses correlate with direct medical costs, informal care, productivity losses and intangible costs.

This research highlights that as disability severity increases, so too does the economic burden. The total cost associated with moderate MS was 70% higher than our estimated cost for those with mild MS; while the cost associated with severe MS was approximately three times the total cost for those with mild MS. This finding is consistent with that reported in the international literature and emphasizes that delaying disability progression should be of paramount importance from an economic, as well as a clinical perspective.

It is also apparent from the findings in this study that people with MS face considerable challenges when it comes to finding and remaining in employment. This is illustrated by the employment rates evident in our study, where 41.7% of men and 43.2% of women report being in paid employment. These figures represent a 24% and a 38% decrease on the national averages for women and men, respectively.

Furthermore, for those who are gainfully employed and experience relapses, or are unable to walk, or who experience extreme fatigue, it can be difficult to sustain a normal working life and indeed, to ensure a decent standard of living. This is apparent in our study where 26% of those in employment, felt it necessary to change jobs due to their condition and close to 70% felt that the disease had limited their career potential, while 61% report not being able to financially provide for their children as much as they would like to.

Since the average age of onset is between 20-40 years, MS impacts on people during the prime of their working lives. This impact manifests in terms of officially reduced working hours, absenteeism and presenteeism. Furthermore, as disability severity progresses, many are forced to permanently withdraw from the workforce due to their condition. This emerged in our study sample, where 27% reported having to permanently withdraw from the workforce as a direct consequence of their disease. Thus, as disability progresses, employment rates for those with MS, rapidly decrease. Moreover and as demonstrated in this report, this happens at a time when average income typically increases, leaving many of those with MS, at an impasse at a point in their lives, when their peers are at their most productive.

This research serves to highlight the considerable work-life challenges associated with having MS in Ireland and the substantial productivity losses associated with such challenges. Particularly striking in this respect is the significant proportion of our study sample that felt it necessary to permanently withdraw from the workforce as a consequence of their condition. While legislation and changes in attitudes mean that workplaces are becoming more disability friendly (MS Ireland) – our findings demonstrate that more could be done to improve employment opportunities and to foster flexible work practices, that may help to enhance the work-life prospects of those living with MS in Ireland. In this regard, the Multiple Sclerosis International Federation's (MSIF) survey of 8,681 people with MS, 5 key factors emerged that according to the respondents, would help keep them in the workplace (Chandraratna, 2010).

1. Stable disease assisted by effective treatment.
2. Supportive employers and colleagues.
3. Seated work
4. Flexible work hours
5. Computer adjustments

For those in our sample, quality of life (as measured by the EQ-5D) was one-third lower than that previously reported for a representative sample of the general population (Kind et al., 1999). This is likely a symptom of disease progression and associated consequences, such as functional impairment and for many, high levels of disability, while compounded further by the increased need for care and for many, abject employment prospects.

Coping with these major challenges, can place many of those with MS under considerable psychological pressure. This too was reflected in our study sample, where 33% reported having received a diagnosis or had been treated for depression since being diagnosed with MS, while 27% reported the same with respect to anxiety. Such levels are significantly higher than those that arise in the general population and point to the conclusion that screening and subsequent treatment for mental health problems should play an important role in the overall management of the disease.

Our results show that MS has a significant economic burden on Irish society. In our study, we estimate that total costs attributable to MS as being €47,683 per person, per year. Our estimate is comparable to previous research in the area. This estimate is in line with the conclusions in previous cost-of-illness studies of MS in in France, Germany, Italy, Spain and the United Kingdom; with total costs ranging from €39,468 to €52,232 per person with MS (Karampampa et al., 2012a).

While there is currently a lack of comprehensive information of the overall prevalence of MS in Ireland, previous Irish research assumes an overall population of people with MS in Ireland as being 8,000 – however our research suggests that this is likely be a conservative estimate. In Chapter 3, we present prevalence estimates in the range of 8,000 to 10,000 and for the purpose of this study and on the basis of the research conducted –we make the assumption there are 9,000 people living with MS in Ireland.

Extrapolating our annual costs per person with MS to the prevalence figure of 9,000 people, we estimate the annual total cost of MS in Ireland as being €429.15 million per annum.

Supplementary to our approach to calculate the costs associated with MS in general, we also estimated the annual cost of MS relapse in Ireland. Doing so provided for an estimate of €4,510 per person experiencing a relapse and extrapolating to the national population of those with MS, provides a total annual cost attributable to MS relapse of €16.9million.

While the overall cost-of-illness estimates serve to highlight the tremendous societal costs associated with multiple sclerosis in Ireland, the range provided also points to the ambiguity inherent in doing so, as currently there is no generally accepted prevalence estimate for MS in Ireland. A more precise estimate could be generated, if Ireland had a national registry of people with MS, or if the HSE made publicly available aggregate statistics of persons with MS who hold medical cards or long term illness cards.

12 Appendix

12.1 List of tables & figures

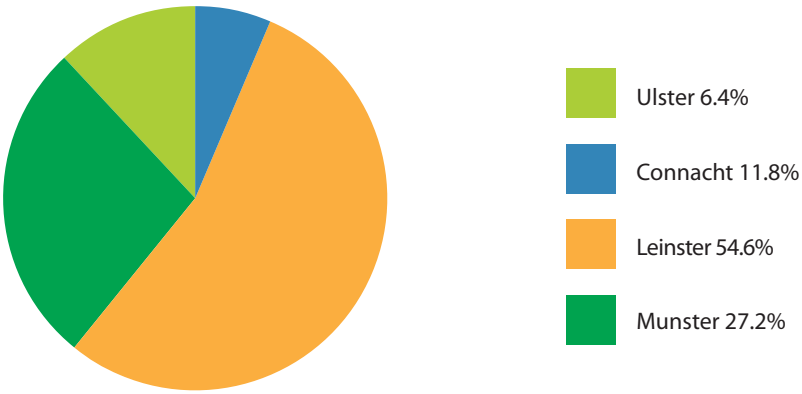


Figure 28 ROI population by province

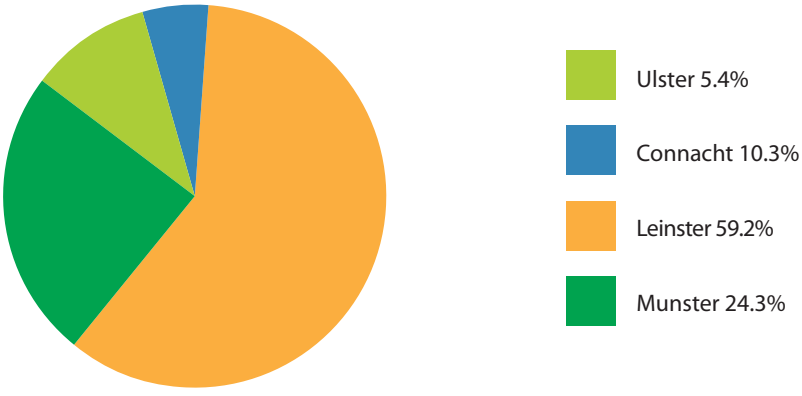


Figure 29 Sample population by province

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(Footnotes)

1 These figures represent the total resource in our study sample, annualised where necessary*.

2 These figures represent the total annual resource extrapolated to the national population of people with MS, assuming a total prevalence of 9,000.

Supported by NOVARTIS

Date of preparation: October 2015