

Title: Timely treatment of Relapses in Multiple Sclerosis: health utility analysis of the *NeuroDirect* integrated pathway.

Keywords: multiple sclerosis, person with multiple sclerosis (PwMS), relapse, telephone triage, EQ5D-5L, health status.

Keypoints

- **Study question:** What impact does a specialist nurse-led telephone assessment/triage service (*Neurodirect* integrated pathway) coupled with standard treatment for significant multiple sclerosis (MS) relapses, have on the EQ5D-5L scores as a measure of health status?
- **Summary answer:** This pathway increases patient health state utility values by 0.15 at 6-8 weeks follow-up.
- **What is known and what this paper adds:** This is the first study of relapses in MS to use the EQ5D-5L health status measurement tool and demonstrates the value of the *NeuroDirect* integrated pathway.

Abstract

The aim of this study was to assess the impact on health status of a multiple sclerosis (MS) nurse specialist telephone assessment/triage (*Neurodirect* integrated pathway) coupled with standard treatment for significant MS relapses. This is an audit-based study of a prospective case series of 108 patients experiencing relapse symptoms who contacted *NeuroDirect*, a National Hospital for Neurology and Neurosurgery telephone assessment service, in the period February 2012 and October 2013. The MS specialist nurse-led teletriage centre applied the EQ5D-5L measure of health related quality of life (HRQoL) at the initial assessment and the planned 6-8 weeks follow-up. The scores were converted into health state utility values (HSUVs). These showed a statistically significant improvement in health status, of 0.15, at 52 days follow-up on average. The study demonstrates that an efficient teletriage relapse pathway, as offered by *NeuroDirect*, with standard clinical care has a clear effect on improving HRQoL, as measured for the first time by the EQ5D-5L in this population.

Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterised by demyelination in the brain, spinal cord and optic nerve. Typical presentations include visual defects, balance difficulties, limb weakness and sensory change. The disease evolution generally involves multiple acute or subacute inflammatory attacks, termed relapses (table 1 and annex 1), which last days or weeks and may result in persistent neurological deficits (NHS, 2014, Brownlee et al., 2016, Lublin et al., 2014). There are estimated to be 7-8000 relapses per annum, generating a substantial economic cost (NICE, 2014, Pike et al., 2012). Moreover, people with MS (PwMS) suffering relapses not only have to access more healthcare resources, but they have a reduced ability to work or participate in family/social activities: all of which results in a lower health-related quality of life (HRQoL) (Jones et al., 2016).

Relapses in MS		
Definition	New symptoms/worsening of existing symptoms that last more than 24 hours in the absence of infection or any other cause after a stable period of at least 1 month.	
Symptoms	Mobility/balance including falls	Speech and swallowing
	Muscle spasms and stiffness	Vision disturbances
	Tremor	Cognitive symptoms
	Urinary and faecal incontinence	Depression and anxiety
	Sexual dysfunction	Sleep disorders
	Sensory symptoms and pain	Fatigue

Table 1. Relapses in MS(NICE, 2014)

Patients with relapses can recover completely or partially, with estimates for the recovery rates for mobility related relapses being about 70% at 6 months, while the remaining third either

require a longer time to recover or have an incomplete recovery (Iuliano et al., 2008). Relapse recovery can be facilitated by administration of high-dose corticosteroids (Goodin, 2014), which in UK practice are usually intravenous methylprednisolone (IVMP), 1 g/day for three days or oral methylprednisolone (OMP), 0.5 g/day for five days (NICE, 2014). Corticosteroid treatment improves the speed of recovery, but has no impact on disease progression and frequency of relapses (Goodin et al., 2002). Disease progression can be influenced by disease modifying therapies (DMTs), particularly in terms of reduction in relapse frequency (Goodin et al., 2002).

The relapse service at The National Hospital for Neurology and Neurosurgery (NHNN) University College London Hospitals (UCLH) Foundation Trust has previously been described (McNicholas et al., 2012) and here we formally evaluate it using a global measure of health related quality of life - the EQ5D-5L instrument. The relapse service comprises a number of major components: the MS nurse specialist telephone assessment/triage, *Neurodirect* integrated pathway (as described below), clinical evaluation in the clinic, corticosteroid treatment and multidisciplinary input from different specialties, such as physiotherapy.

Description of the *NeuroDirect* pathway

NeuroDirect is one component of a larger integrated digital care model that supports PwMS to access timely advice and treatment interventions. The model includes a telephone triage line staffed by MS specialist nurses. Using the service, patients and staff discuss physical, mental, and social care needs and agree on tailored care plans (as explained below). The model facilitates sharing of information across primary and secondary care organisations, and health and social care teams.

The *NeuroDirect* electronic clinical assessment tool provides a framework to guide the MS nurse through areas of relevant clinical history and importance (for example, it includes assessment of 'hidden' symptoms such as altered mood, abnormal bladder function, pain and fatigue) outlined in NICE guidelines (NHS, 2014). It includes ascertainment of possible infection, previous relapse history, disease modifying drug use, symptom management medications, steroid use in the past (efficacy and side effect profile), the possibility of pregnancy that may impact treatment choices, impact of symptoms on psychological wellbeing, daily activity and home life. If the patient is concerned that they are experiencing a relapse, the MS specialist nurses conduct a relapse specific assessment consisting of symptom status (new/worsening), severity and duration of symptoms. The EQ5D-5L questionnaire (Herdman et al., 2011, van Hout et al., 2012) is used as an objective measure of quality of life HRQoL as part of the assessment process in the patient who are deemed to have a relapse.

Following the relapse oriented telephone assessment, a joint decision is made with the person with MS on how best to proceed. Options include: 1) a period of self-monitoring; 2) a GP visit for local assessment and infection screening; or 3) a referral into the relapse clinic for a specialist multidisciplinary assessment. Patients referred into the specialist multidisciplinary relapse clinic are also booked into a planned telephone follow-up clinic 6-8 weeks later. Those attending the relapse clinic would have *significant* relapses, which although subjective, would typically be a moderate-severe motor, sensory or balance disturbance; or a milder impairment which had a significant effect on daily work or family function: an example, would be significant proprioceptive dysfunction in a woman with a young baby.

Randomised controlled trials (RCTs) of patients with other chronic conditions, such as chronic heart failure, show teletriage assessment to increase quality of life as compared to usual care

(Scalvini et al., 2005). Telerriage systems are also associated with high patient satisfaction rate, 55-90% (Turner et al., 2015).

EQ5D-5L Questionnaire

There are many scores used to assess disability in PwMS, both clinician and patient oriented. The most commonly used are the: Extended Disability Status Scale (EDSS), Multiple Sclerosis Impact Scale-29 (MSIS-29) and the Multiple Sclerosis Functional Composite (MSFC) (Kurtzke, 1983, Ontaneda, 2012, Hobart, 2001). However, these are disease-specific, whereas the EQ5D-5L is a generic tool that can be used to compare disability generated by MS with disability generated by other conditions, such as diabetes. Moreover, those described are used to guide clinical response rather than HRQoL, so from a health economics perspective, the EQ5D-5L is more useful.

The EQ5D-5L questionnaire is a validated health status measure developed by the EuroQol Group used to assess and value the current health of participants (Herdman et al., 2011, van Hout et al., 2012). It consists of 5 dimensions that evaluate patient Health Related Quality of Life (HRQoL): mobility, self-care, usual activities, pain/discomfort and anxiety/depression on a scale from 1 – no problems, to 5 – severe disability (annex 2). In economic studies of the cost utility of an intervention the key feature of the EQ5D-5L is the transformation of the health states to a single index value which represents health utility producing an anchored score between 0 (Worst Possible Health) and 1 (Full health). The health status index used is based on sets of weights that have been derived from values from the general population, which implies that these values can be associated to a societal valuation of the respondents' health state.

Methods

EQ5D-5L Questionnaire and Analysis:

The EQ5D-5L data was converted to the index score using the EQ5D-5L: Crosswalk Index Value Calculator (EURO-QO Version 1.0) – box 1. EQ5D-5L profiles were converted into health state utility values (HSUVs) on the day of the first telephone contact and at the 6-8 weeks planned follow-up telephone call. HSUVs range from 0 (Worst Possible Health) to 1 (Full Health). The values are based on a public database made available by the EuroQuol Group who, by using cross-walking technique to produce a preference-based tariff value set evaluated by members of the public, patients and health care professionals (Herdman et al., 2011). The underlying mechanism for describing change in utility score was derived by subtracting post-measurement index score from the pre-measurement score to produce a difference as an overall measure of the effect of the treatment (HSUV difference = HSUV follow-up – HSUV baseline). We evaluated patients' EQ5D-5L scores at the initial *NeuroDirect* call and at a planned follow-up call at 6-8 weeks. However, the final cut-off for our study was placed at mean + 2.5xSD, 70 days, in order to represent 98.5% of the data.

Microsoft Excel v. 2007 and SPSS v.21 were used for the statistical analysis. Paired t-tests and Chi-squared tests were used for numeric data and categorical data, respectively.

Health related quality of life (HRQoL)	Health state utility values (HSUV)	EQ5D-5L profiles
The value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment or policy.	Measure of HRQoL based on generic questionnaires to describe the individual experience of the general population or of patients' experience derived from a treatment/health intervention.	Each EQ5D-5L profile is in the format 11111-55555 (a total of 3125 profiles), from best to worst. Each EQ5D-5L profile corresponds to a HSUV from 1 (best) to 0 (worst).

Box 1. Definitions of health related quality of life, health state utility value and EQ5D-5L profile (Horsman et al., 2003, Van Hout et al., 2012).

Results

Between February 2012 and October 2013, 401 PwMS called the *NeuroDirect* service to report symptoms suggestive of relapse. A total of 108 were triaged through the *NeuroDirect* pathway as significant relapses. The EQ5D-5L questionnaire was measured at baseline and at mean 52 days (+/-7). Six patients with a follow-up later than the chosen cut-off (70 days) were excluded, leaving 102 to be evaluated (Figure 1). 98% of patients (100) received IVMP or OMP as relapse treatment.

The mean time from *NeuroDirect* call to the relapse clinic appointment was 5.4 days (+/- 5.2).

The demographics are shown in table 2.

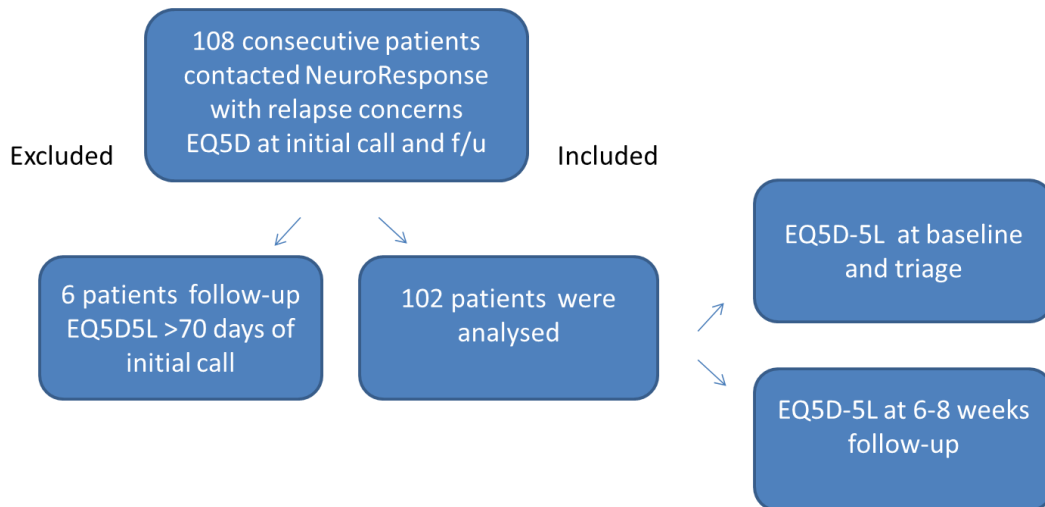


Figure 1. Study design.

Variable		Percentage (absolute value)
Sex	Females	74.5% (n=76)
	Males	25.5% (n=26)
MS type	Relapsing remitting	89.2% (n=91)
	Secondary progressive	4.9% (n=5)
	Primary progressive	3.9% (n=4)
	Clinically isolated syndrome	0.9% (n=1)
	Unknown	0.9% (n=1)
Disease modifying therapy (DMT)	None	55.8% (n=57)
	Avonex	23.5% (n=24)
	Copaxone	10.7% (n=11)
	Rebif	5.8% (n=6)
	Betaferon	0.9% (n= 1)
	Azathioprine	0.9% (n=1)
	Other	1.8% (n=2)
Urinary tract infection	Absent	86.2% (n=88)
	Present	3.92% (n=14)

Table 2. Baseline characteristics of the study group.

In addition to a neurologist and MS nursing input, the main other multidisciplinary input was physiotherapy (50%)

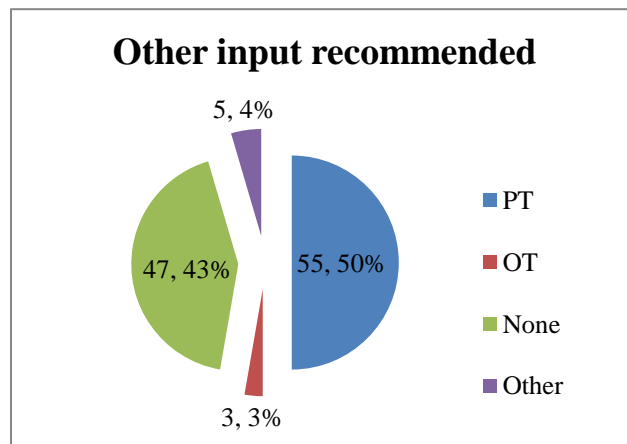


Figure 2. Additional input recommended for PwMS and an active relapse. OT – occupational therapy, PT – physiotherapy

EQ5D-5L

The overall utility value for the study group at baseline was 0.42 and at 6-8 weeks follow-up 0.58. There was a 0.15 improvement which was statistically significant - $p < 0.0001$. Figure 3 shows the individual differences between the utility values at baseline and follow-up. Of note, 83 (81%) patients had an improvement in health utility values, while only 19 had a decrease.

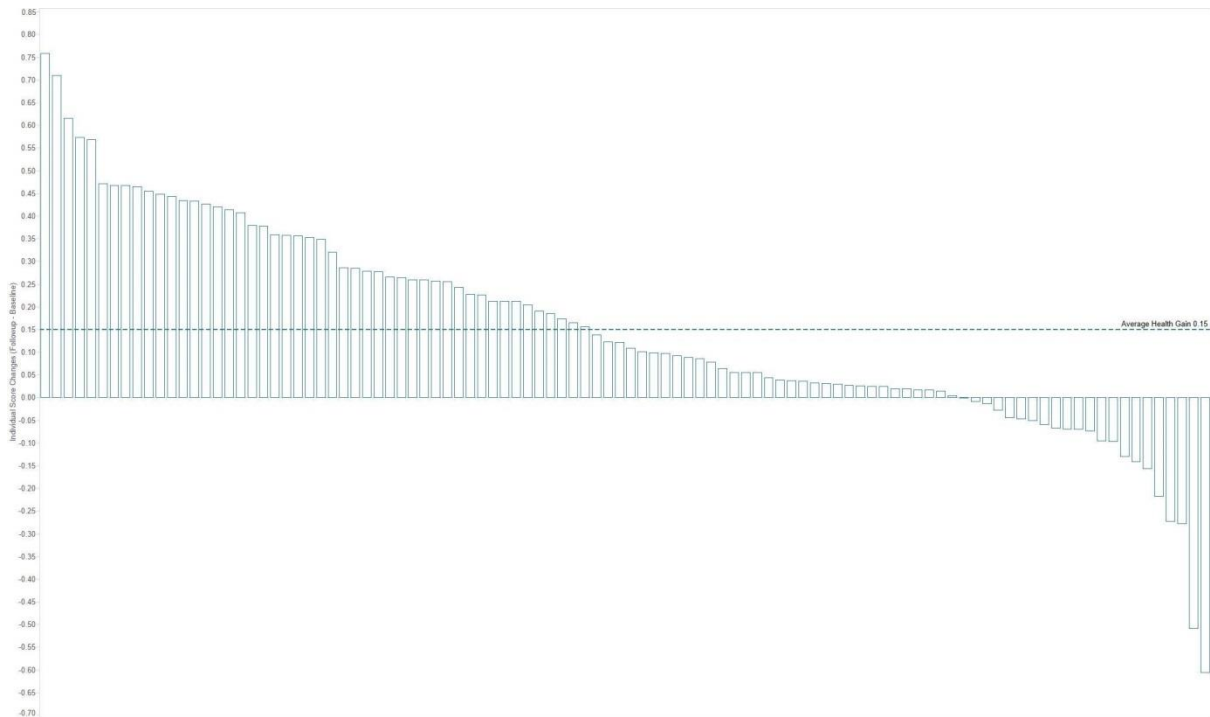


Figure 3. EQ5D-5L utility values at initial call and 6-8 weeks follow-up. HSU difference for each patient in the study group, sorted in order of effect. The average improvement was 0.15

(trendline) *** - $p < 0.0001$

A breakdown of scores based on the EQ5D-5L items shows a marked improvement in mobility, usual activities, pain/discomfort and overall scores. The improvement is less evident in anxiety/depression and self-care (Figure4). The overall change in EQ5D-5L scores is driven principally by mobility, as most patients had a severe state (score of 5) at baseline, but a moderate state (score of 3) at follow-up. This overall trend is recapitulated in each of the dimensions with more patients in the normal and mild health states (score 1 and 2) at follow-up than at baseline. Simultaneously, the number of patients in the severe and disabling health states (scores 4 and 5) decreases at follow-up.



Figure 4. The EQ5D-5L dimensions at baseline (before) and 6-8-weeks follow-up (after) for (a) anxiety/depression, (b) self-care, (c) pain/discomfort, (d) mobility and (f) usual activities show the percentage of patients in each category (0-5). Patients generally migrate from higher (worse) score at baseline (4/5) and demonstrate an improvement, recording less severe scores (1/2) at follow up. This is most evident in mobility.

There was no significant difference between patients who were on Disease Modifying Treatments (DMTs) - HSU score difference 0.16, and those who were DMT naïve – 0.14, $p=0.68$; or between patients who received physiotherapy input - 0.17, and patients who did not - 0.14, $p=0.56$.

Discussion

The National Institute for Health and Care Excellence recommends that relapse treatment be started within 2 weeks of symptom onset (NICE, 2014). A telephone triage system, such as *NeuroDirect* can be an efficient and effective way of improving specialist coordinated care access for PwMS experiencing relapses. The mean time from *NeuroDirect* call to specialist attention was 5 days, well within the 14 days recommended by the NICE guidelines.

The novelty of this study is the systematic measurement of the EQ5D-5L, pre and post assessment and treatment. It is the recommended generic tool to assess health technologies, health services used to prevent and treat diseases (NICE, 2008). Indeed, EQ5D-5L been shown to be a reliable generic psychometric tool for other medical conditions such as type 2 diabetes (Koh et al., 2016, Cheung et al., 2016), and it is currently used as a standard for the development of new disease-specific psychometric tools (Hill et al., 2016, Morley et al., 2016).

EQ5D-5L is the latest version of the most widely accepted HRQoL measure and has only been used by 4 studies of UK cohorts of MS patients to date (Wang et al., 2016, Yfantopoulos and Chantzaras, 2016, Khan et al., 2016, Shiroiwa et al., 2016, Fogarty et al., 2013, Herdman et al., 2011). These studies show an inverse correlation (predictive power of regression $R^2=0.48$) between the utility values derived from the EQ5D-5L generic health assessment tool and the principal MS-specific disability scale used to assess motor impairment in patients with MS, EDSS (Hawton and Green, 2016, Fogarty et al., 2013, Orme et al., 2007, Parkin et al., 2000). Conversely, one study has questioned the use of generic tools in assessing patients with MS, finding a poor correlation between the EQ5D-5L and the patient generated index (PGI) - an individualized measure for quality of life (Kuspinar and Mayo, 2013). However, this study used

the earlier version, the EQ5D-3L, and only enrolled patients with a mild to moderate motor disability, precisely the range for which the EQ5D-5L shows improvement in discrimination power.

Our study shows a statistically significant improvement of 0.15 in HSUV, from 0.42 to 0.58, after *NeuroDirect* teletriage and treatment. Interestingly, cross-sectional studies of MS populations in the UK have comparable HSUVs of 0.49 – 0.59 (Orme et al., 2007, Fogarty et al., 2013). This would suggest that our endpoint, EQ5D-5L, is no different from a general MS population. However, these two studies do not distinguish between patients in remission from those in relapse. A more accurate comparison of our outcome is to remission HSUVs of 0.604 – 0.610 in patients who did not experience any relapses in the past 6 months (Parkin et al., 2000, Hawton and Green, 2016). This result is in accordance with our remission HSUV of 0.58 at 6-8 weeks follow-up, and, therefore represents a stable outcome for the following 4 months for these MS relapse patients.

Relapses in MS can be precipitated by infections, such as urinary tract infections (UTIs) (Buljevac et al., 2002, Correale et al., 2006) and a pathway has been described and is followed by our service (Phe et al., 2016). In the present study, the rate of UTIs was low (4%), indicating that the majority of relapses had not been triggered by an infection.

This is an example of a service complex intervention, with the main components impacting on improvement being time to assessment, relapse severity, corticosteroid use and therapy input. These can only be analysed in a qualitative way outside an RCT structure. We demonstrate that this model of service (structured teletriage) leads to quick evaluation of the PwMS (52 days) and that a therapy intervention (mainly physiotherapy) is used in about half of the relapses. Clearly

all of these factors, and others, will have an effect on improving the HSU. However, further study into the components of teletriage systems is warranted to dissect the role of the MS specialist nurse-led assessment and the other factors, such as DMT usage, and subsequent allied health professional therapy input. Moreover, the cost-effectiveness of an elective telephone assessment system could be directly compared to non-elective admissions to the emergency department in this group of patients.

We also demonstrate an improvement in the individual dimensions of the EQ5D-5L. The greatest changes were in mobility, usual activities and pain with significant numbers of patients converting from high disability scores to little/no disability scores. The study of EQ5D-5L in MS (Fogarty et al., 2013) indicates that it is these three dimensions that are most affected by relapses. Of note, anxiety/depression level seems to be the least responsive dimension of the EQ-5D-5L. One explanation for this is the high prevalence of background depression and anxiety in PwMS with observed prevalences of anxiety being 9-36%, and depression 20% (Marrie et al., 2015, Marck et al., 2016) as opposed to rates of 5% and 16%, respectively, in the general population (Hausleiter, 2009). We conclude that the higher background levels of anxiety/depression in this population are unlikely to reduce with relapse improvement, but are manifestations of a chronic, long-term condition.

Conclusions

The present study focuses on a specialist relapse integrated pathway and its impact in managing PwMS by streamlining the coordination of care in this subset of patients. We have shown that a teletriage relapse pathway for PwMS (*NeuroDirect*) with all the associated clinical service measures (corticosteroid treatment, physiotherapy input and follow-up) improves HRQoL as measured for the first time by the global standard EQ5D-5L, from HSUVs of 0.42 to 0.58. We also present the changes in the EQ5D-5L individual dimensions in order to gain insight into the role disease-specific measurements play in generic HRQoL analysis.

Key elements of the *NeuroDirect* teletriage model are now being developed in the scaling-up of a larger integrated digital care model across several UK regions. We anticipate that it has the potential to improve the health and reduce the cost of care of people with other neurological conditions.

Permissions

As the present study was based on an internal service audit, ethical approval was not required.

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Annex 1 – NeuroDirect Relapse definition and questionnaire

The Commissioning Policy for Multiple Sclerosis (England) has defined relapses as clinically significant and or clinically disabling to assess the impact of the relapse on the individual.

Clinically significant relapse	Clinically disabling relapse
(any of the following)	(one or more of the following)
<ul style="list-style-type: none">• Any motor relapse• Any brainstem relapse• A sensory relapse if it leads to functional impairment• A relapse leading to sphincter dysfunction• Optic neuritis• Intrusive pain that lasts more than 48 hours	<ul style="list-style-type: none">• It affects the patient’s ability to work• It affects the patient’s activities of daily living as assessed by an appropriate method• It affects motor or sensory function sufficiently to impair the capacity or reserve to care for themselves or others as assessed by an appropriate method• The individual needs treatment/hospital admission as a result of the relapse

The NeuroDirect team work within the definitions of clinically significant and clinically disabling relapses to assess impact and ask a number of questions including:

- What symptoms have occurred?
- Are they new symptoms or a return of old ones?
- What effect are they having on your daily living?
- When did they start?
- Do they fluctuate or are they constant?
- Do you have any signs of infection?
- When was last relapse? How was it treated?
- Are you taking a disease modifying drug?
- Have you missed any doses?
- Are you taking any other medication?
- Are you pregnant or recently given birth (appropriate)?
- How would you like to manage this episode?

Annex 2 – EQ5D-5L Questionnaire

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

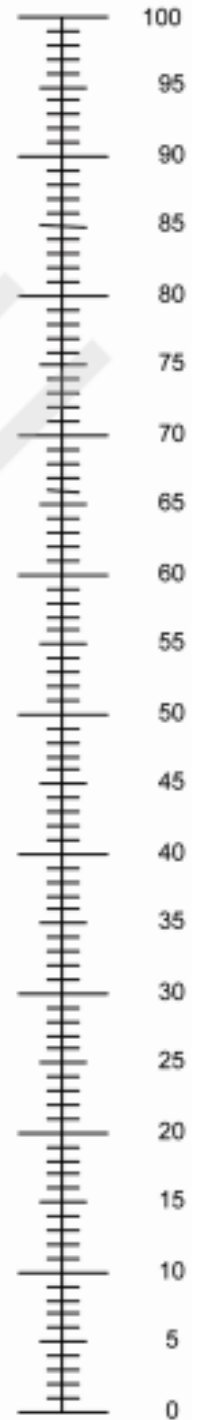
ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

