**Appendix G – patient/carer organisation statement template**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**

**Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis**

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

**About you**

**Your name:** [redacted]

**Name of your organisation: MS Society**

**Are you (tick all that apply): Director of Policy and Research**

**About MS**

Multiple sclerosis (MS) is one of the most common disabling neurological conditions affecting young adults. Around 100,000 people in the UK have MS. For most people, MS is characterised by relapses followed by periods of remission, while for a minority it follows a progressive pattern from onset. However, even those with relapsing-remitting MS typically experience increasing disability and morbidity with entry into the secondary progressive phase. Genetic risk is well established with >57 genes now identified that drive the primary inflammatory response; and environmental triggers are also indirectly implicated. Although much progress has been made in identifying disease modifying treatments, these are not curative and even the most effective carry significant risks for treated patients. The progressive phase of MS remains refractory to treatment and this represents the main unmet need for affected individuals with this variable, unpredictable but threatening disease.

**About the MS Society**

The MS Society is the UK's largest charity for people living with MS, with approximately 38,000 members and 300 branches. The MS Society is the UK's largest charitable funder of research into MS. Since 1953 the MS Society has been providing information and support, fighting for change and in 1956 funded our first research project. We provide grants to individuals, for example in order to make home adaptations. We are committed to bringing high quality standards of health and social care within reach of everyone affected by MS

This submission has been prepared by the MS Society's Policy and Research directorate and is informed by:

- the results of an online survey - over 1000 people affected by MS told us about their views and experiences in relation to MS disease modifying drugs (DMDs) and relapses;
- a semi structured interview with an expert patient who has direct experience of taking alemtuzumab;
- secondary research into the costs of MS, and;

- clinical trial data from the CARE-MS I and CARE-MS-II, involving 563 and 628 people with relapsing remitting MS respectively, and a five year follow up study of the phase II CAMMS233 trial involving 198 people.

The following four appendices are attached to this submission:

- **Appendix A:** Transcript of interview with a patient expert
- **Appendix B:** A report on the perspectives of people with MS on relapses and disease modifying drugs.
- **Appendix C:** Free text responses to an open question on experiences of relapses and/or disease modifying drugs;
- **Appendix D:** Interview questions sent to the patient expert in advance of the interview.

**Executive Summary**

The clinical trial results show that alemtuzumab is highly effective at reducing relapses - appearing to be superior, in terms of relapse reduction, to a standard first line therapy; and highly effective at reducing disability progression. Alemtuzumab therefore has the potential to improve clinical outcomes and quality of life for a significant number of people with MS and to save the NHS and personal social services money.

**Reduction in risk of confirmed progression of disability**

The two year CARE MS II trial demonstrated that alemtuzumab significantly reduced the sustained accumulation of disability progression by 42 per cent compared with interferon beta 1a in patients who have relapsed despite first line treatment. During the trial 20 per cent of those on interferon beta 1a experienced worsening disability compared to 13 per cent of those taking alemtuzumab.

A five year follow up of study of patients on the Phase II CAMMS223 clinical trial have shown that alemtuzumab can have an impact on disability progression for up to five years – lowering the risk of sustained accumulation of disability by 72 per cent.

The potential to maintain function and have a greater quality of life are critically important, especially for a potentially debilitating condition such as MS that may move from the relapsing-remitting to the secondary progressive phase and for those who have a high risk of accumulating disability.

**Reducing relapses**

Relapses have a physical and sometimes debilitating impact on people with MS; the majority of people with MS felt relapses left them unable to do the things they wanted to do (95 per cent), slowing them down (98 per cent). As a result, 90 per cent of people with MS told us that they cannot be as independent as they want to be, with 58 per cent always or often relying on others for support.

Alemtuzumab has been shown in both the CARE MS I and CARE MS II to have a greater clinical effect on the rate of relapse than current first line DMTs, which reduce relapses by approximately 30 percent:

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In the Phase III CARE MS I trial those taking alemtuzumab were around 55% less likely to experience a relapse over the course of two years (40% people taking interferon beta 1a experienced a relapse compared with 22% taking alemtuzumab).

The results of the Phase III CARE MS II trial demonstrated that those taking alemtuzumab were around 50% less likely to experience a relapse over the course of two years (51% of people taking interferon beta 1a experienced a relapse compared with 35% taking alemtuzumab).

The five year follow-up study found that alemtuzumab reduced the rate of relapse by 69 per cent compared to interferon beta 1a.

**Key concluding messages**

The impact of the degree by which alemtuzumab has been shown to reduce relapse rate and disability progression should not be undervalued given the devastating effect that relapses and disability progression can have on an individual's quality of life. Approving alemtuzumab would increase the treatment options that people with MS have, which would maximise the possibility that people find a treatment that works for them, both in terms of efficacy and tolerance to adverse effects.

If alemtuzumab was not made available on the NHS, it would have the following implications for people affected by MS:

- Fewer people will receive treatment that works for them – many may not be treated at all, with an obvious impact on health outcomes.

- Even those receiving current disease modifying treatments will experience more relapses, worsening disability and a loss of quality of life than if they were able to take alemtuzumab.

- Fewer people with MS will be able to continue in full time employment. This means they would be less productive, and would need to rely on the welfare system sooner;

- People with MS would be more reliant on a carer and therefore less independent. People with MS would not be able to do the things they wanted to do and would feel physically limited by their condition as their MS progressed faster; carers will also experience poorer health and a loss of quality of life.

- Care and support costs met by the NHS and personal social services will be higher. The more people experience relapses and the resulting disability associated with it, the more people with MS will increase their reliance on NHS and social care services.

- People with MS will experience poorer mental well being. Currently two thirds of people with MS experience anxiety and/or depression. Anxiety is more common for relapsing MS and depression is more common for progressive MS.

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**What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?**

**1. Advantages**
**(a)** Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

Alemtuzumab is a significant development in the treatment of relapsing-remitting multiple sclerosis (RRMS). In addition to significantly reducing annualised relapse rates it has also been shown to reduce the risk of disability progression for those with relapsing MS in comparison to interferon beta 1a, which has shown to be sustained over a five year period. Current disease modifying treatments (DMTs) available for RRMS are administered through monthly infusion, highly frequent and ongoing sub-cutaneous or intramuscular injections, or (for a small number of people) a daily oral treatment. Alemtuzumab comprises of one course (a daily infusion for five days) followed by a second course 12 months later (a daily infusion for three days), and in a declining number of cases a third or fourth course (same as the 2$^{nd}$) after a further 12 months or more. We already see alemtuzumab having a considerable impact on health outcomes and quality of life for many of the people who have been able to take it with consequent benefits to the health care system and the taxpayer. Alemtuzumab has the potential to offer a vital additional option for people with MS and an important alternative to current DMTs for RRMS.

Alemtuzumab has undergone two phase III clinical trials – CARE MS I and CARE MS II. These trials, which involved 1191people with MS globally, aimed to investigate the effect of alemtuzumab on:

- annualised relapse rate
- time to six month sustained accumulation of disability
- various surrogate MRI brain scan indicators of tissue damage associated with MS

A further five year follow-up study of those on the phase II CAMMS223 trial, involving 198 people with MS, investigated the long-term safety and efficacy of alemtuzumab compared to interferon beta 1a in early active RRMS. The study provided evidence on the long-term effect of alemtuzumab on relapse rate and accumulation of disability.

The trials found that those taking alemtuzumab experienced the following benefits in comparison to interferon beta 1a:

**1. A lower annualised rate of relapse**
A relapse is defined as an episode of neurological symptoms, which lasts for at least 24 hours and occurs at least 30 days after the onset of any previous episode. In relapses, symptoms usually come on over a short period of time but often remain for a number of weeks – usually three to four - and can sometimes last for months. People with MS can experience a wide-range of distressing and debilitating symptoms from fatigue to visual impairment, mobility problems to cognitive problems. Relapses can vary from mild to severe. At their worst, acute relapses may need hospital treatment, but many relapses are managed at home, with the support of a

GP, MS specialist nurse, and other healthcare professionals. Although some people recover from relapses and experience complete remission, around half of all relapses leave residual problems; another important reason to reduce the frequency and severity of relapses.

Due to the varied and unpredictable nature of MS, determining an 'average' relapse rate is not straight forward; considering the number of people currently on disease modifying drugs it is estimated that a significant proportion of individuals with relapsing remitting MS experience one or more relapses per year.

Alemtuzumab has been shown in both the CARE MS I and CARE MS II to have a greater clinical effect on the rate of relapse than current first line DMTs, which reduce relapses by approximately 30 percent:

The two year randomised controlled CARE MS I study investigated the efficacy and safety of first line alemtuzumab compared with interferon beta 1a. The results demonstrated that alemtuzumab significantly reduced relapses by 54.9 per cent compared with interferon beta 1a. During the course of the trial 40 per cent of people taking interferon beta 1a experienced relapses compared to 22 per cent of people taking alemtuzumab. Further analysis of the data showed that 78 per cent of those on alemtuzumab were relapse free at two years compared to 59 per cent of those on interferon beta 1a.

The two year randomised controlled CARE MS II study investigated the efficacy and safety of alemtuzumab compared to interferon beta 1a in individuals who had relapsed despite first line treatment. The results demonstrated that annualised relapse rates were significantly reduced by 49.4 per cent. During the course of the trial 51 per cent of people on interferon beta 1a experienced relapses compared to 35 per cent of people taking alemtuzumab. Further analysis of that data showed that at two years 65 per cent of those taking alemtuzumab were relapse free compared to 47 per cent of those taking interferon beta 1a.

The five year follow-up study found that alemtuzumab reduced the rate of relapse by 69 per cent compared to interferon beta 1a.

**2. Reduction in risk of confirmed progression of disability**

The majority of people with MS experience a progression of disability over the course of the condition. It is estimated that approximately 65 per cent of people with relapsing remitting MS will eventually go on to develop secondary progressive MS 15 years after being diagnosed and 10-15 per cent are affected by primary progressive MS. Progressive forms of MS are characterised by a sustained accumulation of disability independent of relapses. This progression occurs at varying rates and can lead to a worsening of symptoms resulting in a permanent loss of mobility and the need to use a wheelchair, cognitive damage and permanent sight loss. There is also a real risk of accumulating disability for those with RRMS who are refractory to first line treatment.

The MS Society knows that addressing disability progression is a major issue for people with MS and currently represents an unmet treatment need. Our new

Research Strategy (2013-17) highlights research into progression as a major priority for the MS Society going forward. The strategy was formed in consultation with people affected by MS and the MS research community. It was approved by our Board of Trustees - the majority of whom are people affected by MS, either directly or as carers. It should be noted that many years ago, in the 1990s, the MS Society funded an early clinical trial into the use of alemtuzumab as a potential treatment for MS. We do not though have any financial stake in the product.

As well as greatly reducing the incidence of relapses, alemtuzumab appears to reduce the risk of disability progression, and therefore has the potential to increase quality of life over the medium to long term, for a significant number of people with MS who still experience relapses.

The CARE MS II trial demonstrated that alemtuzumab significantly reduced the sustained accumulation of disability progression by 42 per cent for those with first line treatment refractory RRMS in comparison to interferon beta 1a. During the trial 20 per cent of those on interferon beta 1a experienced worsening disability compared to 13 per cent of those taking alemtuzumab.

Clinical trials into alemtuzumab have shown that it can have an impact on disability progression for up to five years (five year CAMMS223 follow-up trial) – lowering the risk of sustained accumulation of disability by 72 per cent. We know from our consultation that this is an important aspect that people with MS would like treatments to address.

The rate of sustained disability accumulation did not differ between those on alemtuzumab and those taking interferon beta 1a in the CARE MS I trial.

Proving a benefit in terms of disability progression is notoriously difficult; but without at all minimising the difficulty of living with relapses, a product that has shown significant benefit here would be greatly valued by people affected by MS. The potential to maintain function and have a greater quality of life is of critical importance, especially for a chronic, long-term and potentially debilitating condition such as MS that so often evolves from relapsing-remitting MS to the secondary progressive phase.

**(b)** Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:
- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above

Patients can expect to gain the following benefits from using alemtuzumab:

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**Reduction in accumulation of disability**
Many of those who are refractory to current first line treatment are advised to stay on the same course of treatment despite ongoing disease activity or are switched to another treatment with similar efficacy. It is not surprising then that the majority of people with relapsing forms of MS are not receiving disease modifying treatment at all. For these individuals there is a risk of both more relapses and accumulating disability if they are without effective treatment, which could have serious implications on their quality of life and their ability to remain active and independent members of society. Alemtuzumab has been shown to be highly effective as a first and second line therapy and has been shown to reduce the risk of sustained accumulation of disability, over a five year period.

**Quality of life (lifestyle, activities of daily living, independence)**
A drug which can significantly reduce the number of relapses and disability progression is likely to have a considerable positive impact on the quality of life of the individual. People with MS have told us that relapses have a physical, mental and sometimes debilitating impact, affecting their ability to do day-to-day activities and significantly reducing their quality of life. In our survey, 95 per cent had experience of relapses that left them unable to participate in routine activities of daily living, nearly 90 per cent said they could not fulfil their usual roles and responsibilities and a further 98 per cent of people felt that relapses slowed them down.

People with MS reported that they wanted to avoid and prevent relapses from occurring as they resulted in a loss of independence. Respondents described relapses as 'set backs.' As one person put it, "*I want to be normal again and not have to endure debilitating relapses several times a year which set me back so far and mean I have to rely on others to help me, when I just want to be able to do the things that everyone else takes for granted*" (quote 259, appendix C).

The inconvenience and "paraphernalia" required to inject, especially when on holiday was remarked upon by many of the respondents. One person explained that "*one airport official asked what I felt was unnecessarily intrusive questions*" (quote, 110, appendix C) Another explained that, "*it [injecting] does involve planning when going on holiday as a fridge is needed in hotter climates, airlines need to be notified and delivery company contacted*" (quote 158, appendix C). Another related the impact to business travel: "*work wise, business travel is more of a concern when I have to manage a three times a week injection schedule*" (quote 42, appendix C).

**Physical Symptoms**
Prior to alemtuzumab our patient expert experienced new symptoms on a weekly basis, "*In 10 months I must've had about 20 different symptoms. Most of them were sporadic."* As a result of alemtuzumab she has experienced a significant improvement in all her symptoms, including pain. She no longer suffers from tingles, muscle spasms and cramps and all her old symptoms have, "*more or less disappeared overnight*." Occasionally our patient expert still experiences old symptoms when she is working too hard but does not experience any new symptoms. Consequently our patient expert feels she is able live life normally.

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**Mental health**

Alemtuzumab's effectiveness at reducing relapse rates and disability progression could significantly improve the mental well-being of people with MS. The emotional and psychological impact of a relapse and increase in disability should not be underestimated. Approximately two thirds of people with MS suffer from depression and/or anxiety due to both the physical changes caused by MS and the strain of living with such physical uncertainty[1]. Suicide is also more common in people with MS than the general population.[2] Alongside this, many people with MS do not get the emotional support that they need, with only 51 per cent of those who needed emotional support able to get it. One respondent provided a useful insight into the emotional impact of a relapse and the resulting loss of independence and increased dependency on family: "*Relapses are not only worrying, painful and distressing at the time but can take a considerable amount of time to recover from. I have been left with residual problems from every relapse I have had and then the worry of if I have another, is the disease progressing quicker than I thought - that is always a worry at the back of my mind. I then worry about the impact on my husband and that he has to take time off work to help me. The concern that he will not cope if I become severely affected by another relapse is a genuine worry as he gets extremely frustrated with the whole MS scenario. As a very independent lady, this adds its own issues to my state of mind and the fact that I cannot be there as readily for my children and colleagues*" (quote 55, appendix C).

**Helping people with MS to remain in work**

In an MS Society survey we found that, at some point, a relapse had prevented 82 per cent of people with MS from carrying out their work duties (paid employment) and that a further 89 per cent were unable to fulfil their usual roles and responsibilities during a relapse. Over half of the respondents reported that a relapse often or always has an impact on their ability to carry out their work duties.

The impact of relapses on people's ability to work can be significant as the responses to our survey illustrate. *"Relapses make sustaining full time work so much more difficult as they make each day such an effort and I am exhausted, although I still manage to hold down a full time job*". Another commented that she "*had two relapses, one straight after the other. These relapses can be very debilitating and take away your independence. I work part time and when I have to have time off sick I feel I am letting people down. I am currently undertaking light duties as my mobility is not what it was. This greatly upsets me as I feel that due to MS, I am unable to do the job that I have enjoyed for many years*" (quote 291, appendix C).

The difficulty of holding on to a job during a relapse was commented on by many of the respondents who either took annual leave to help cope during a relapse, or needed to take months off work to recover. The next two examples illustrate both of these scenarios:

"*I was diagnosed in 2007 and have had three relapses since. I am a clerical assistant and when I have a relapse, I lose vision in my left eye (optic neuritis). I have pain in*

[1] A large scale study of anxiety and depression in people with MS: A survey via the web portal of the UK MS Register, Jones et al (2012)

[2] ibid

*my arm, leg, back and chest. The first relapse caused me to be off work for 8 months. The second relapse caused me to be away from work for 4 months. The most recent relapse was – in the words of my doctor – nipped in the bud. The five day treatment of steroid infusion was a great benefit to me and I was only away from work for one week. I only work part time now as the fatigue forces this as when I am tired, I have more apparent cognitive issues at home and work. I also stumble on a daily basis as my balance is very poor*" (quote 265, appendix C).

"*I work full time for the NHS as an occupational therapist. To do this properly, I have to lose all aspects of life – I can't clean my home, go out and sometimes can't even make myself a cup of tea as I am so exhausted. I try to limit the impact at work by taking annual leave instead of sick leave if I feel I am losing energy which means I spend a lot annual leave in bed recovering from work*" (quote 84, appendix C).

The survey findings support the argument that relapses make continuing in a permanent job a challenge for some people living with MS. For example, one commented "*I am lucky that I have an understanding employer who has agreed for me to work from home part of the week when I am having problems (mobility wise). This I have found very useful from a fatigue point of view as well as allowing me to continue to work*" (quote 388, appendix C).

Some people had a less than positive experience with their employers as a result of an accumulation of relapses: "*I have had four bad relapses in the last 14 months causing me to have to take 6 months off work in total. I have now been made redundant and wonder if it was because of the disability?*" (quote 161, appendix C)

It is evident that relapses and an increase in disability progression can and do have a significant impact on people's ability to work. Unemployment among people with MS is higher than in the general population. A report by the Work Foundation[3] found that up to 80 per cent of people with MS stop working within 15 years of the onset of the condition. It also found that up to 44 per cent of people with MS retire early due to their condition – a higher percentage than the European average (35 per cent) and that more than 75 per cent of people with MS report that the condition has impacted their employment and career opportunities. An MS Society survey (2013)[4] found that of those who are of working age only 25 per cent were employed compared to 75 per cent of the wider UK population. A drug which could reduce the frequency and severity of relapses enabling people to continue in a permanent job with fewer disruptions to their day to day life would not only improve people's productivity when at work, but would allow more people with MS to stay in work for longer. This would then cost the taxpayer less in terms of the number of people becoming reliant on the welfare system and improve quality of life for people with MS and their carers.

**Positive impact on carers**

People with MS also rely on support from family and/or friends to help them to manage the impact of having MS, to help them remain independent and lead a fuller life. This includes support with everyday tasks like washing and dressing and getting

[3] Ready to Work? Meeting the Employment and Career Aspirations of People with Multiple Sclerosis, The Work Foundation (2011)

[4] A lottery of treatment and care – MS services across the UK, MS Society (2013)

out and about. At times of relapses and as disability progresses the need for this support increases and the impact on carers can be greater. Our survey on the needs of people with MS found that out of the 10,530 people with MS who responded 71 per cent received care, support or assistance from a friend of family member. Thus the effect of MS does not only affect the life of the person with the condition but can also significantly impact on family members and/or friends. A treatment such as alemtuzumab that has been shown in clinical trials to reduce relapses by approximately 50-55 per cent and disability progression by 40 per cent would therefore reduce the burden on the patient and the carer and is also likely to reduce management costs associated with MS.

A loss of independence as a result of a relapse can make people with MS more dependent on others for help. In our survey, 90 per cent of people with MS felt they could not be as independent as they wanted to be, 91 per cent of people with MS said that they had to rely on other people for help during a relapse and a further 93 per cent felt they were a burden on their family at some point during a relapse.

72 per cent of people agreed that administering an injection by themselves was difficult. The inconvenience of having to rely on others to inject as they couldn't inject themselves was highlighted in the responses as a problem. One respondent commented: "*It has never got any easier to inject or to ask my husband to do it for me. Indeed it can cause friction between us because we both get anxious*" (quote, 42, appendix C).

**Choice of treatment**

Since 2002, people with MS have been able to inject MS disease modifying drugs (DMDs). In 2007, Tysabri (natalizumab) was approved for those with rapidly evolving severe relapsing-remitting MS. People with MS who are taking Tysabri need to attend hospital to receive regular infusions. In 2012 Gilenya (fingolimod), the first oral pill for MS, was approved by NICE - a second line treatment for people with highly active RRMS, which requires them to take a pill on a daily basis. We are greatly concerned that despite the availability of these treatments there are a significant number of people currently not on any DMDs. In a recent MS Society report[5] which surveyed 10,530 people with MS, we found that 60 per cent of people with relapsing forms of MS were not taking any of the seven disease modifying treatments currently available.

Alemtuzumab should increase the choice of treatments for people with relapsing forms of MS, potentially as a first line option as well as for people for whom current standard DMDs would not be appropriate due to treatment failure, side-effects or lack of tolerability.

It is clear from the results of our survey and from people's experiences, that relapses can be an unpleasant and debilitating feature of living with MS, with long lasting physical and psychological effects on not only people living with MS but their carers too. Any drug that is more effective than the current DMDs at reducing the risk of sustained accumulation of disability and reducing relapse rates has the potential to

[5] A lottery of treatment and care – MS services across the UK, MS Society (2013)

transform the lives of people living with MS and their ability to have a greater quality of life.

**2.Disadvantages**
Please list any problems with or concerns you have about the technology. Disadvantages might include:
- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer)

The adverse events associated with alemtuzumab, which were identified during the clinical trials, particularly during the administration of this treatment included: infusion reactions, infections, thyroid disorders and immune thrombocytopenia or ITP (an autoimmune condition associated with a lowered platelet count) - regular blood tests are required to monitor this. Three patients on alemtuzumab developed cancer of the thyroid which was also treated. There was one fatality caused by ITP in a previous phase 2 clinical trial of alemtuzumab. Investigators subsequently changed monitoring procedures to screen for this unexpected side effect, and have not had a fatality associated with ITP since. Although there are a number of treatable side-effects some which, while uncommon or even rare, are serious. ITP is serious but treatable; more rarely, Goodpasture's syndrome is far more difficult to treat. A further disadvantage identified by the patient expert interviewed by the MS Society is that although the treatment itself is only administered once a year, these potential side effects mandate regular blood tests, even well beyond the treatment period.

**3.** Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

The MS Society is not aware of any differences in opinions between patients about the usefulness of alemtuzumab.

**4.** Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

The MS Society expects this technology to benefit people with relapsing-remitting MS. We do not know of any subgroups of people with relapsing-remitting MS who would benefit more or less from the technology.

**Comparing the technology with alternative available treatments or technologies**
NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

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The MS Society is aware of the following current disease modifying drugs used to treat relapsing remitting MS as standard practice: Avonex, Rebif, Betaferon, Extavia, Copaxone, Tysabri and Gilenya.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

The advantages of alemtuzumab over other first line licensed treatments for MS (Avonex, Rebif, Betaferon, Extavia, Copaxone and Tysabri) can be categorised as follows:

**- Effective at reducing disability progression:** On the CARE MS II trial, people with MS were around 42 per cent less likely to experience disability progression over the course of two years. Over five years, alemtuzumab has been shown to lower the risk of sustained disability by 72 per cent.

**- More effective at reducing relapses than current first line treatments for RRMS:** On the trials, people with MS were between 50 and 55 per cent less likely to experience a relapse in comparison to interferon beta 1a over a two year period. This clinical effect is greater than for current first line DMDs, which generally reduce relapses by approximately 33 per cent.

**- Improved treatment adherence:** Due to the mode and frequency of administration of alemtuzumab issues such as treatment adherence and compliance associated with the current standard DMTs will be less of a problem.

**- Improved lifestyle and quality of life:** The possibility of having an MS drug administered only twice via infusion with the possibility of a third course of treatment will potentially significantly increase the quality of life of individuals with MS. People with MS would be more independent as they would not need to rely on others to help them to inject. They would also have fewer relapses and would therefore experience fewer disruptions to their working life, enabling them to stay in employment for longer. There would be no long-lasting social visibility of treatment as only two and possibly three infusions are required. It would also give people with MS greater freedom particularly when travelling. Current treatments need to be refrigerated and require administrative preparation when travelling abroad.

**- Less dependent on carer:** A treatment such as alemtuzumab that has been shown in clinical trials to reduce relapses by approximately 50-55 per cent and disability progression by 40 per cent would therefore reduce the burden of care and support on the carer as well as the patient.

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The personal experience of people with MS who have tried current first line treatments for RRMS and the impact it has had on their lives are discussed below. These findings are taken from our survey on the perspectives of people with MS on relapses and disease modifying drugs.

1. Injection site reactions as a result of highly frequent injections

Skin indentation and a growing inability to cope with regularly injecting were a common theme amongst respondents, including an increase in difficulty when injecting over long periods. One person stated: "*It is getting more and more uncomfortable to inject as the original sites around my body are now dented inwards and are now unsuitable for injection. I have contacted my MS nurse who has given me ideas on suitable places to inject…the sore injection sites rub on my clothes during the day*" (quote 239, appendix C).

Most people who completed the survey found regularly injecting an unpleasant experience; 87 per cent of people with MS on DMDs at some point felt uncomfortable injecting with over 55 per cent of people finding it always or often uncomfortable to inject. A complaint among some respondents was the effect of scar tissue and fat atrophy, including injection site ulcers. Others complained that constantly injecting was not sustainable: "*injections are not a long term solution – there are only so many sites a body can put up with...*" (quote155, appendix C).

In some cases, complications with injection sites have resulted in emergency admissions. "*One experience I had about two years ago involved an injection site becoming infected causing a cyst on my stomach. When the pain became excruciating I ended up in A&E at 2am having it lanced under local anaesthetic. This resulted in me having weeks off work (unpaid), a district nurse having to visit every day to dress the wound and I believe the incident triggered a relapse which has since left me unable to use my right hand to write with ever since.*" (quote, 283, appendix C).

2. Pain and stress associated with regular injections

Respondents pointed to a relationship between the length of time spent injecting and a heightened sense of anxiety. As one respondent put it: "*the stress and anxiety caused by injections has almost as much effect on my quality of life as the MS condition itself*" (quote, 267), another described it as a "*three-weekly dread*" (quote 26, appendix C). Some respondents described how they had tried to deal with the anxiety of injecting, which they claimed had caused them to develop a 'needle phobia.'

A common theme amongst respondents was a perception that their MS symptoms exacerbated difficulties associated with injecting. One explained how "*the injections are difficult with the numbness in my fingers and hands*" (quote 311, appendix C). Similarly, another described the difficulty of injecting without a steady hand: "*it [injecting] begins to control your life…it is against human nature to hurt yourself and even more tricky when trying to inject with a tremor*" (quote 53, appendix C

Respondents described how injecting during a relapse made them feel worse about living with their MS: "*I initially thought when I started injecting I would not have so*

*many relapses but in reality, I still get them although I tell myself that I get less now. I hate injecting through a relapse because of the effort and the feeling of they are not working so why bother putting myself through the trauma. I have not missed an injection but it is more my wilful nature than what I want to do*" (quote 73, appendix C).

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

The disadvantages of the technology compared to current treatments include:

**- Side-effects:** The clinical trials demonstrated that side-effects such as infections and thyroid disorders were more common in those taking alemtuzumab than those receiving interferon beta 1a. Alemtuzumab is also associated with more serious side-effects, for example, ITP. However these are uncommon and in most cases treatable. Our patient expert H reported that the side effects were at their most intense whilst she was in hospital. However H says she felt fine within two to three months of being discharged. The potential side-effects of alemtuzumab and the risk of developing other autoimmune conditions was a concern for H but "*having gone through a year of really aggressive MS, none of the side-effects sounded worse than what I had already gone through…The risks were significant but set against the idea that this wasn't a condition that was going to go away. I was still having symptoms. I was still being reminded on a daily basis that I had MS. I thought…if it helps with the symptoms and if it means that this is as bad as it's ever going to get them I was willing to give it a go*" The side effects of taking alemtuzumab should be weighed against the advantages in terms of reducing relapses and delaying disability progression.

**Research evidence on patient or carer views of the technology**
If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

The MS Society conducted a semi structured interview with an individual who had experience of taking alemtuzumab. The interview has been transcribed and anonymised. The transcripts of the interview can be read in full in appendix A and a copy of the interview questions is included in appendix D. The personal experience of a person with MS who has taken alemtuzumab and the impact it has had on their and their partner's life is discussed below. In addition to this interview, we have regular contact with other people who have and are taking alemtuzumab.

**Course and/or outcome of the condition**

H did not expect alemtuzumab to do anything else beyond freezing the condition where it was at: "*I wanted to make sure that my condition got no worse and potentially slightly better… I was thinking of the long-term – this was the first time that any treatment I had ever been offered that had the potential long-term benefits as well as immediate benefits…If we can stop it at this point, we know we can cope with it…but if my condition continued to progress at the rate and the way it had following diagnosis then it would've been untenable. I don't know what the end-point would've been but it wouldn't have been a good place*."

"*It felt like alemtuzumab was giving me my life back. It was giving me a chance of having the life I had prior to diagnosis and without alemtuzumab I wasn't certain about what my life would've ended up being…Saying yes to alemtuzumab was less terrifying than living with MS untreated for the rest of my life…I could see a point where it would become untenable to live with and I didn't want to get to that point*."

**Quality of life (lifestyle, work, social functioning etc)**

Prior to MS, H reports life before MS as being "*relatively normal, happy and fulfilled life*." She and her partner both worked full time and "*used every opportunity to experience life and have fun*." However, when H was first diagnosed with MS, "*It stopped my life, absolutely dead stop…the accumulation of symptoms and the fatigue had already started having an impact on how we were living our lives about 18 months before the diagnosis…We didn't go out. We didn't enjoy ourselves. It was horrific. It was like living through months and months of hell*." As well as her social life coming to an end H also had to take two months off work after diagnosis and then resigned a few months later as she just couldn't continue working. H says she is now "normal" and for her MS has become "*a minor irritation that I have to take into account occasionally.*" She says: "*It [alemtuzumab] gives me control of my life. I work full-time. I never thought at the time of diagnosis that I would be working…It has given me my life back*." Her partner also noted that he couldn't "*remember the last time I needed to get concerned…It's brought our life back to as it was before diagnosis…We don't feel like our lives are constrained anymore…It really does just feel like a normal life*."

**Physical symptoms**

Prior to alemtuzumab H's MS was quite active with new symptoms cropping up on a weekly basis, "*In 10 months I must've had about 20 different symptoms. Most of them were sporadic."* As a result of alemtuzumab H has experienced a significant improvement in symptoms. She no longer suffers from tingles, muscle spasms and cramps and all her old symptoms have, "*more or less disappeared overnight*." H says she still does experience some symptoms, although no new symptoms, but they are manageable and she sees them more as warning signs that she is over-doing it: "*If I'm experiencing symptoms I know I need to have time off. It's [alemtuzumab] given me more control of my MS*." This improvement was not expected by either H or her partner or the medical team – the effectiveness of the treatment came as a surprise.

**Mental health and well-being**

When H was diagnosed no support was offered nor any information on MS. This led to H and her partner feeling very isolated and alone as they were left to cope with the diagnosis on their own. H became depressed, increasingly withdrawn, as the

awareness of what the implications of the diagnosis could be set in and was in a state of denial regarding her diagnosis. Consequently she was cut off from family and friends, which meant the "*burden of support fell squarely on Adrian's shoulders*." H said, "*I probably wouldn't be here, alive, if he hadn't been with me*."

The diagnosis of MS also had an impact on H's partner: "*I struggled…I think I was certainly suffering from a degree of stress, which resulted in physical symptoms. I started to feel unwell and I wasn't able to sleep. We were heading downhill physically and for me, as a result of the stress of the situation and the unknowns – not having the support and because Helen was very withdrawn. We both ended up very isolated and feeling that really it was the two of us in the world*." H's partner also had to take a lot of time off work to care for H.

**Views on current first line treatments**

H was not offered any disease modifying treatment for her MS when diagnosed and fell into a state of depression and denial. Once H began to come to terms with her condition she began to consider her treatment options and realised beta interferon was her only option. She questioned whether beta interferon would fit into their lives, given she would need to inject several times a week. For them, "*beta interferon didn't seem to be that effective…and the side-effects of beta interferon seemed to be as bad as the some of the symptoms H was suffering. It seemed very marginal as to whether there would be any benefit to beta interferon*." H found the side-effects "*horrifically off-putting. It seemed the treatment was worse than the condition."* She also said it was a "*daily or once a week reminder that you're a sick person*." On this basis H refused to take current first line treatments. She also declined to participate in an earlier comparison clinical trial on alemtuzumab as there was a possibility that she would be randomly allocated to the interferon beta 1a group.

H believes that the choice of treatments for those newly diagnosed is limited and offers no hope. For those who are newly diagnosed H says there is "*so much isolation, so much despair about whether it is normal, whether it is going to continue*" and that "*alemtuzumab and the new drugs that are coming out really are a glimmer of hope of people being able to see beyond that treatment to a life where their condition will be manageable. I think putting people even slightly more control in of their condition is so important because they are going to be living with it until they die."* MS "*takes over people's lives and becomes all that they are and I think alemtuzumab gives people a chance to be somebody who just happens to have MS rather than being MS themselves."*

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

The MS Society is not aware of any adverse effects that were not apparent in the clinical trials.

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**

**Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis**

*Perspectives of people with MS on relapses and disease modifying drugs.* MS Society, April 2010

**Availability of this technology to patients in the NHS**
What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

**1. People with MS would experience fewer relapses and a reduction in disability progression compared to standard first line disease modifying therapy.** This would have the following impact on patients and/or carers:

- Enable people with MS to stay in employment for longer with fewer disruptions. People with MS could then contribute to the economy for longer, reducing the need for people to depend on the welfare system;

- Lower the costs to the NHS and personal social services as more people with MS will experience fewer relapses and a reduction in disability progression. This would reduce the need to rely on these services as much whilst also limiting the number of emergency admissions and appointments to see healthcare professionals either because of injection site complications;

- People with MS would be less anxious about experiencing another relapse. This would improve their mental and physical health more generally, giving people with MS the confidence to lead a full life and a better quality of life;

- People with MS would be less reliant on a carer and be more independent. People with MS would stand a better chance of being able to do the things they want to do, rather than feeling physically limited by their condition

**2. Alemtuzumab would give people with MS and their carers an improved quality of life.** This would have the following impact on patients and/or carers:

- Fewer relapses and reduced disability progression would reduce the burden of care and support on the carer as well as the patient.

- People with MS would have more choice about the treatments they take - weighing up efficacy, side effects and convenience. Alemtuzumab offers an alternative treatment choice for people with relapsing MS

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

If alemtuzumab was not made available on the NHS, it would have the following implications for people affected by MS:

**1. People living with MS would experience more relapses and an increase in disability progression compared to those receiving standard disease modifying treatments**. This would have the following impact on patients and/or carers:

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- Even those receiving current disease modifying treatments will experience more relapses, worsening disability and a loss of quality of life than if they were able to take alemtuzumab, including loss of mobility and eyesight, pain, fatigue and cognitive impairment;

- Fewer people with MS will be able to continue in full time employment. This means they would be less productive, and would need to rely on the welfare system sooner;

- People with MS would be more reliant on a carer and therefore less independent. People with MS would not be able to do the things they wanted to do and would feel physically limited by their condition as their MS progressed faster;

- Increase the costs to the NHS and personal social services. The more people experience relapses and the resulting disability associated with it, the more people with MS will increase their reliance on NHS and social care services.

- People with MS would be increasingly anxious and depressed about relapses and the disability associated with them.

**2. Without an alternative, people with MS will be limited in choice to existing treatments**:

- Fewer people will receive treatment that works for them – many may not be treated at all, with an obvious impact on health outcomes.

- Treatment options will continue to involve significant planning and disruption to every day life.

- Significant numbers of people with MS will continue to stay dependent on others

It is vital that, with an increasing number of alternatives entering the market for the treatment of relapsing remitting MS, people with MS have access to the right drug for them at the right time and there should be a focus on the potential to maximise quality of life for the individual.

Are there groups of patients that have difficulties using the technology?
The MS Society is aware of the following groups of patients who should not be using the technology:
- Those who are pregnant
- Patients who have cancer
- Patients who have had chemotherapy for cancer
- Patients with progressive MS, without relapses

**Equality**
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

**Other Issues**

Please consider here any other issues you would like the Appraisal Committee to consider when appraising this technology.