**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: Multiple Sclerosis Trust**

**Are you (tick all that apply):**

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- ✓ an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)

  **Director of Service Development**
- other? (please specify)

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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.

The MS Trust is in contact with over 40,000 people affected by MS; people with MS, their families, friends and the health care professionals. A major component of our work is supporting people with health-related issues and enabling informed decision making.

MS is commonly diagnosed between the ages of 20 and 40. Approximately 80% will be diagnosed with relapsing remitting MS (RRMS). We speak daily to people who are dealing with issues relating to relapsing remitting MS: coping with the impact of diagnosis, choosing which treatment to take, understanding and balancing risk/benefit profiles, dealing with difficulties of self-injection or side effects, and coping with physical and financial consequences of relapses.

A treatment which either eliminates or reduces the frequency and severity of relapses is a major benefit for people affected by relapsing remitting MS.
Alemtuzumab offers

- highly effective first line treatment for early active MS
- highly effective second line treatment for treatment for those failing first line DMTs
- greater efficacy at reducing relapse rates compared to current DMTs
- no evidence of disease activity and improvement in disability levels in some patients
- consequent avoidance of residual disability
- reduction in asymptomatic lesions
- innovative treatment regime, in most cases just one or two treatment courses

Through our enquiry service we are only too aware of the devastating impact MS relapses can have both in the short and long term. MS relapses are unpredictable in onset, severity, type of symptoms, and duration. Recovery is often incomplete, leading to accumulation of disability with each successive relapse. Residual disability may be apparent, such as impaired mobility, but may also be less overt, such as depression, fatigue, cognitive problems or sexual dysfunction. The more invisible consequences of a relapse can often be overlooked by health professionals, family and work colleagues yet impact on quality of life and capacity to remain in employment as profoundly as more apparent symptoms.

Relapses have a significant impact on the ability to work, leading to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in financial burden, for the individual, their family and the state. With frequent relapses or the impact of accumulated residual disability, remaining in work can become impossible and unemployment amongst those with RRMS is high. Relapses can also have a profound effect on a person's daily activities, social life and relationships and present considerable psychosocial and emotional challenges for both the individual and for family and friends.

Recovery from a relapses often relies on access to MS rehabilitation. In a cash-strapped NHS, the reality is that services to support people coping with a relapse, such as physiotherapy or the provision of equipment or carers, are often limited or non-existent. The quality of and access to care is highly dependent on where someone lives. Individuals contacting the MS Trust frequently report that the urgent access to physiotherapists or occupational therapists necessitated by a rapid onset of symptoms is rarely possible. A

recent caller to our enquiry service reported a 10 week waiting list to see a physiotherapist for treatment of walking problems following a relapse. As well as prolonging the effect of the relapse on someone's life, these delays risk compounding problems, introducing further distress to the individual and cost to the NHS.

Research evidence supports the treatment of people with relapsing remitting MS early in the disease to prevent axonal damage and irreversible disability. Current practice in the management of RRMS is active and acknowledges that even if people with MS continue to have relapses while on therapy, they may still be deriving benefit from the treatment. State of the art approach to treating relapsing remitting MS aspires to minimal or no evidence of disease activity – including absence of relapses and absence of asymptomatic lesions on MRI. In clinical studies, alemtuzumab has achieved freedom from disease activity in 24% of patients with highly active MS.

**(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

**1. Relapse reduction**
Alemtuzumab reduces relapse rates in early active relapsing remitting MS. Open label and phase II studies have established that alemtuzumab is less effective in later stages of MS.

In CARE-MS I (treatment-naïve), alemtuzumab reduced the relapse rate to 55% of that seen in people taking interferon over the two years of the trial. 78% of people in the alemtuzumab group didn't have a relapse during the two years of the trial compared with 59% of the interferon group.

In CARE-MS II (continued relapses while taking beta interferon), the relapse rate of those on alemtuzumab was reduced to 49% of that seen in people taking interferon over the two years of the trial. 65% of people in the alemtuzumab group didn't have a relapse during the two years of the trial compared with 47% of the interferon group.

**2. Reduction in disability progression**
In CARE-MS II alemtuzumab significantly reduced the risk of sustained accumulation of disability by more than 40% compared to beta interferon 1a.

**3. No evidence of disease activity**
In an analysis of CARE-MS I, alemtuzumab-treated patients were more likely to be free of clinical disease activity, MRI activity and overall disease activity than beta interferon- treated patients. *Giovannoni G, et al. Disease activity-free status in CARE-MS 1 phase 3 study. Annual Meeting of the European Neurological Society, Prague, Czech Republic, 09.06.12 - 12.06.12, O288.*
http://registration.akm.ch/einsicht.php?XNABSTRACT_ID=150959&XNSPRACHE_ID=2&XNKONGRESS_ID=165&XNMASKEN_ID=900

In a subset analysis of CARE-MS II data, those with highly active MS (2 or more relapses in year before study and 1 or more baseline gadolinium-enhancing lesion), freedom from relapses, MRI activity, and sustained accumulation of disability was achieved by 24% of patients on alemtuzumab and 0% of those on interferon. *Krieger S, et al "Alemtuzumab is efficacious in highly-active RRMS patients in CARE-MS II" CMSC-ACTRIMS 2013; Abstract DX01.*
*https://cmscactrims.confex.com/cmscactrims/2013/webprogram/Paper1191.html*

**4. Quality of life**
In CARE-MS I and CARE-MS II alemtuzumab treated patients reported improved quality of life. *Selmaj K, et al. Alemtuzumab improves patient-reported quality of life in relapsing-remitting multiple sclerosis: CARE-MS I and II phase 3 trials. Annual Meeting of the European Neurological Society, Prague, Czech Republic, 09.06.12 - 12.06.12, P 338.*

**5. Convenience of administration**
Alemtuzumab treatment consists of an iv infusion on 5 consecutive days, followed by iv infusions on 3 consecutive days, 12 months later. In most cases, no further treatment is required. The short course of therapy may be preferred by patients and result in decreased overall service usage.

## 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 thier family (for example cost of travel needed to access the technology, or the cost of paying a carer)

**1. Side effect profile**
Two serious side effects have been reported during alemtuzumab treatment:

- Overactive or underactive thyroid gland, leading to thyroid-related side effects, was seen in 15-20% of participants in both of the phase III studies. These side effects are treatable but in general use are likely to require careful monitoring and lifelong thyroid medication. A clinical trial which aims to reduce the incidence of thyroid side effects with palifermin is underway.
- Idiopathic thrombocytopenic purpura (ITP) affected approximately 1-3% of clinical trial participants. One person died of ITP during a phase II study, after which strategies were put in place to ensure that future cases were recognised early.

Other common side effects seen in clinical trials have been:
- Infusion-related reactions such as headache, rashes, fever and nausea.
- Infections including coughs, colds, chest infections and herpes virus infections (such as cold sores or shingles).

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

We are not aware of any. From discussions with people who are newly diagnosed, the majority with relapsing remitting MS expect to start treatment early. There will always be

individual preferences about route of administration, benefit and risk balance and practicalities linked to daily routines. We are aware that a significant proportion welcomes the potential for no evidence of disease activity with alemtuzumab treatment.

**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?

We are submitting this response in advance of publication of full prescribing information from the EMA and without in depth knowledge of any subgroup analysis that may have taken place on the clinical data.

We anticipate that alemtuzumab will be licensed as a treatment for active relapsing remitting MS, defined by clinical or MRI features. The details of clinical or MRI features have not been published. Clinical studies with alemtuzumab indicate that it was particularly effective in early, active disease; for an individual it will be important to identify those most likely to benefit from its greater efficacy despite a greater risk of side effects.

A common topic of our discussions with people with RRMS relates to difficulties associated with self-injection. The novel treatment regime of alemtuzumab will be a significant benefit for those concerned about routine self-injection and avoids many of the potential adherence problems with self-administrated preparations.

**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.

The current drug therapies that are available as first line treatments are:
Avonex - interferon beta 1a
Betaferon and Extavia - interferon beta 1b
Rebif - interferon beta 1a
Copaxone - glatiramer acetate
Tysabri - natalizumab
Gilenya - fingolimod. Approved by NICE as a second line treatment when relapse rates remain unchanged or increase despite at least 12 months beta interferon treatment.

(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)

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Beta interferons and glatiramer acetate reduce relapse rates by approximately 30% compared to placebo. In phase III studies, alemtuzumab reduced relapse rates by approximately 50% compared to beta interferon 1a. The greater efficacy, novel treatment regime of alemtuzumab and freedom from flu-like and injection site side effects will be significant advantages.

Natalizumab is approved by NICE for people with rapidly evolving severe MS. Natalizumab and alemtuzumab have not been compared in head-to-head clinical trials. We would expect this group to continue to be treated with natalizumab. Many do talk to us about their concerns about the risk of PML, particularly those who are JCV positive and approaching two years of treatment. Alemtuzumab may be an acceptable alternative for these people.

Fingolimod is approved by NICE as a second line treatment only after 12 months of beta interferon treatment. Access to fingolimod is hampered for those on treatments other than beta interferon. We would urge NICE to ensure that the technology appraisal for alemtuzumab does not introduce further roadblocks in treatment pathways.

(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).

Serious side effects of alemtuzumab (over or under active thyroid gland, ITP) will need to be monitored for at regular intervals for some years after last infusion and if they occur may require life-long treatment.

**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.

Taking any drug in the context of a clinical trial, with greater attention from health professionals, will be different from taking it in routine NHS care. Given the novel treatment regime of alemtuzumab, there is a risk that people may become disconnected from MS services. MS nurses and other MS professionals will have a key role in monitoring for side effects and continue to have a key role in managing other symptoms that individuals may experience as part of their MS. People will need to be informed about side effects and closely supported to ensure early reporting of any relevant symptoms.

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

None that we are aware of. Alemtuzumab has been used to treat people with MS "off-licence" and no additional side effects have emerged.

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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.

*Bevan S, et al. Ready to Work? Meeting the Employment and Career Aspirations of People with Multiple Sclerosis. Work Foundation: London; 2011*
*http://www.theworkfoundation.com/DownloadPublication/Report/289_289_MS3.pdf*

- This report highlighted the problems faced by people of working age in the UK and showed that people with MS lose an average of 18 working years, with many dropping out of employment very rapidly after diagnosis.

*MS Society. A lottery of treatment and care – MS services across England and the UK. MS Society: London; 2013*
*http://mslottery.mssociety.org.uk/wp-content/uploads/2013/04/England-ms-lottery.pdf*

- Across the UK, only 40% of those that are eligible are taking a disease modifying treatment.

*Multiple Sclerosis International Federation. MSIF survey on employment and MS. MSIF: London; 2010*
*http://www.msif.org/about-ms/day-to-day-living-with-ms/employment-education-and-ms/employment-and-ms-survey.aspx*

- Having stable MS was rated as the most important factor enabling people with MS to remain in work. Disease modifying treatments were listed as one of the top five factors enabling people to remain employed.

*Pfleger CC, et al. Social consequences of multiple sclerosis (1): early pension and temporary unemployment - a historical prospective cohort study. Multiple Sclerosis 2010;16(1):121-126.*

- 50% of people with MS will be unemployed within 10 years of diagnosis

**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?

Both greater efficacy and novel dosing schedule of alemtuzumab represent an innovative addition to the treatmentoptions for relapsing remitting MS. MS remains a cause of severe disability for many young adults. Current first line treatments have demonstrated effectiveness at reducing relapses but the greater efficacy of alemtuzumab would undoubtedly be beneficial. The novel treatment regime would have a major impact on the quality of life of the person with MS and their families and friends; reduced relapses and less disability have profound personal benefits for quality of life, employment and active participation in society.

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

Highly active MS and non-responders to current first line treatments represent a significant burden for the NHS, to the economy and to carers in the short term to support relapses, since these require steroid treatment, time off work, and can require significant care to be provided to the individual in relapse. In the long term, since relapses can result in individuals accumulating disability, there are significant NHS-related costs in caring for more severe MS, including the potential for increased A&E attendance, hospital admissions and treatment –

sometimes in ITU; provision of expensive equipment such as wheelchairs; as well as the potential loss of economic activity of family members caring for people with MS.

If alemtuzumab is not made available to patients on the NHS, this will severely limit the treatment options available to those with active relapsing MS, particularly those at greater risk of developing PML with natalizumab.

Are there groups of patients that have difficulties using the technology?

None that we are aware of.

**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.

None.

**Other Issues**

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

The terms of the licence granted to a drug will have an impact on the guidance issued by NICE. In MS, this has created de-facto patient sub-groups (eg highly active despite treatment or rapidly evolving severe) which may not reflect clinical reality and introduced roadblocks in the treatment pathway. There is considerable risk that this landscape could be further complicated as new drugs are appraised. First and second lines may not be easily demarcated and those not responding to initial treatment may not have timely access to more effective drugs. We urge NICE to consider how this could be resolved in the best interests of patients and the NHS.

Clarification of the relationship between any or all of the drugs being appraised to the currently available DMTs and the opportunity to review the increasing complexity of the prescribing landscape for DMTs would be welcome.