Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Advice
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In response to an enquiry from the Strategic Planning and Clinical Priorities Team, Planning and Quality Division, Scottish Government

Autologous haematopoietic stem cell transplant for patients with highly active relapsing remitting multiple sclerosis not responding to high-efficacy disease modifying therapies

Advice for NHSScotland

Where patients understand and are willing to accept the demands, risks and uncertainties of treatment, autologous haematopoietic stem cell transplant (AHSCT) should be considered as a treatment option for patients with relapsing-remitting multiple sclerosis (RRMS) who have evidence of significant inflammatory disease activity that has not responded to adequate treatment with licensed high-efficacy disease modifying therapies (DMTs).

The evidence for efficacy and safety of AHSCT in patients with RRMS is from a collection of single-arm observational studies and one randomised controlled trial that has limitations in terms of its applicability to current standard of care in Scotland. Robust cost-effectiveness analysis is not available.

There should be equity of access across Scotland to the procedure and to appropriate follow-up.

Haematological centres offering AHSCT should have multi-disciplinary expertise in the management of multiple sclerosis, clear protocols for patient selection, and be appropriately accredited.

Enrolment of patients into clinical trials is encouraged wherever possible and outcomes of all procedures undertaken should be submitted to relevant audits/registries. Consideration should be given to developing Scottish national audit.

NHSScotland is required to consider the Scottish Health Technologies Group (SHTG) advice.

What were we asked to look at?

We were asked to look at the evidence surrounding autologous haematopoietic stem cell transplant (AHSCT) for patients with highly active relapsing remitting multiple sclerosis (RRMS) not responding to high-efficacy disease-modifying therapies (DMTs).

Why is this important?

The annual incidence rate of multiple sclerosis in Scotland is 8.64 cases per 100,000 people, which represents a high incidence relative to other countries. Of the total cases, around 85% of patients have the relapsing remitting form of the disease.

A number of high-efficacy drug treatments have been approved for the treatment of relapsing remitting multiple sclerosis (for example ocrelizumab, alemtuzumab, natalizumab) but these therapies do not always work. For patients with highly active disease not responding to disease-modifying therapies, AHSCT may have a role in reducing disease progression.

What was our approach?

We produced SHTG Advice based on a review of published literature on the clinical effectiveness and safety of AHSCT compared with DMTs. Our advice incorporated studies on the patient experience of the AHSCT procedure, alongside patient views gathered through our patient organisation submission process. We also looked for published literature on cost effectiveness and compared the costs of the procedure with costs of DMTs. Information on our SHTG Advice product can be found here.

What next?

Our advice will inform strategic planning decisions by the National Services Division of NHS National Services Scotland, NHS Boards and the Scottish Government.

Key points from the evidence review

- No evidence directly comparing the benefits and risks of autologous haematopoietic stem cell transplant (AHSCT) with current high-efficacy disease-modifying therapies (DMTs) in patients with relapsing remitting multiple sclerosis (RRMS) was identified.
- One randomised controlled trial (n=110) compared AHSCT with DMTs in patients with RRMS which remained highly active despite treatment with DMTs. Alemtuzumab and Ocrelizumab were not comparators in this trial. Mean follow-up for this preliminary analysis was 2.8 years. The primary outcome was time to disease progression and assessment of this was blinded. AHSCT significantly prolonged time to disease progression compared with DMTs, hazard ratio (HR) 0.07 (95% confidence interval (CI) 0.02 to 0.24, p<0.001). The profile of DMTs to which patients had been exposed prior to consideration for AHSCT in this trial was different from current Scottish practice.
- A systematic review and meta-analysis of uncontrolled observational studies with median follow-up of up to six years reported that AHSCT for patients with RRMS (seven studies n=414) was associated with a 2-year rate of disability progression of 7.8%. Transplant–related mortality was 1.0% (95% CI 0.4% to 2.6%).
- In addition to the mortality risk, the AHSCT procedure is associated with a range of serious adverse effects commonly including infections, gut symptoms, liver toxicity, neurological problems, kidney injury and effects on blood coagulation. It is also associated with longer term risks, such as infertility, development of secondary autoimmune conditions, and malignancy. High-efficacy DMTs are also associated with a range of serious adverse effects. No evidence was identified directly comparing the benefits and risks of AHSCT with current high-efficacy DMT.
- No relevant cost-effectiveness analyses were identified in the literature and de-novo cost-effectiveness modelling was considered unfeasible owing to the limitations in the clinical evidence base. The average cost of AHSCT specifically for MS patients at a specialist centre in England is £28,200. Based on this estimate, after accounting for savings made from reduced DMT use, re-admissions and maintenance treatment, the net budget impact of AHSCT to the NHS in Scotland is expected to be approximately £650,000 in year 1 (based on 37 patients treated) rising towards £4 million in year 5 (based on 203 patients treated). There is considerable uncertainty surrounding the likely uptake rate of AHSCT, and the unquantified costs of long term disease management, social care and multi-disciplinary care.
- Patient organisations emphasised the devastating impact of MS at an individual, family and societal level, and highlighted the inequity in access to AHSCT between NHSScotland and NHS England. The importance of ensuring equitable access to AHSCT within Scotland was also noted.

Committee considerations

- Evidence is lacking on comparisons of AHSCT with high-efficacy DMTs such as ocrelizumab and alemtuzumab. Trials are in progress, including the UK STAR-MS trial, which may resolve the considerable uncertainty around the comparative efficacy and safety of AHSCT with high-efficacy DMTs.
- The committee recognised that there is preliminary evidence that, for some patients, AHSCT may slow disease progression and improve quality of life but noted that, in discussion with the patient, these benefits needed to be weighed against the significant risks of the procedure. It was noted that AHSCT is a one-off treatment.
- The committee acknowledged that not all high-efficacy DMTs are suitable for all patients, owing to issues of contraindication, safety and availability. There should be equity of access across Scotland to licensed MS drugs.
- There is inequity in provision between NHSScotland and NHS England. AHSCT treatment is available in NHS England as a third-line treatment for people with RRMS who have failed high-activity licensed DMTs, are prepared to accept the significant risks of the procedure, and are eligible under European Group for Blood and Marrow Transplantation (EBMT) guidelines.
- EBMT 2019 guidelines recommend that AHSCT should be offered to patients with RRMS with high clinical and magnetic resonance imaging (MRI) inflammatory disease activity (at least two clinical relapses, or one clinical relapse with Gd enhancing or new T2 MRI lesions at a separate time point, in the previous 12 months) despite the use of one or more lines of approved DMTs.
- Data collated by the Scottish HSCT network indicates that at least 32 patients from Scotland have travelled abroad for self-funded AHSCT.
- Incidence of MS in Scotland is high and varies across the country. Planning for provision of AHSCT should take account of the particularly high prevalence of MS in the North of Scotland including Orkney and Shetland.

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Research question

What is the clinical effectiveness, cost effectiveness and safety of autologous haematopoietic stem cell transplant for patients with highly active relapsing remitting multiple sclerosis not responding to high-efficacy disease-modifying therapies?

Literature search

A systematic search of the secondary literature was carried out between 2 April 2019 and 4 April 2019 to identify systematic reviews, health technology assessments and other evidence-based reports. Medline, Embase, Cinahl, Web of Science, and Cochrane databases were also searched for systematic reviews and meta-analyses.

To ensure that the most up-to-date studies were captured, the primary literature since the most recent systematic review was systematically searched between 2 April 2019 and 4 April 2019 using the following databases: Medline, Embase, Cinahl and Web of Science. A search for qualitative studies of patient experience of AHSCT was conducted between 3 June and 10 June 2019. Results were limited to 2012-2019 and English language.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials. Websites of organisations related to this topic, for example the Association of British Neurologists, and the MS Society UK were also searched.

Concepts used in all searches included: h(a)ematopoietic stem cell transplant, stem cell therapy, autologous stem cell transplant, multiple sclerosis. A full list of resources searched and terms used is available on request.

Introduction

Multiple sclerosis

Multiple sclerosis (MS) is a chronic, disabling, immune-mediated, demyelinating and degenerative disease of the central nervous system (CNS)[1]. The disease usually starts during young adulthood[2]. It causes a wide range of symptoms including: intense pain, deadening fatigue[3], problems with memory, sight, speech and swallowing, arm and leg sensations and impaired movement, bladder and bowel function and balance[4].

Approximately 80-85% of cases of MS are relapsing remitting illness (RRMS)[5]. A relapse is a discrete episode of neurological dysfunction due to acute inflammatory demyelination within the CNS[6]. Over time, the effect of repeated injury to the CNS leads to irreversible and progressive neurological dysfunction and patients enter a secondary progressive disease phase (SPMS). In around 10-15% of patients, the progressive neurological dysfunction starts from the onset of the illness. This is referred to as primary progressive multiple sclerosis (PPMS)[6].

Standard treatment – disease modifying therapies

Standard treatment for multiple sclerosis is disease modifying therapy (DMT) to prevent relapses, new brain and spinal cord lesions, and worsening neurological disability[5]. DMTs include beta-interferon, dimethyl-fumarate, glatiramer acetate, fingolimod, teriflunomide, alemtuzumab, cladribine, ocrelizumab and natalizumab. The route (subcutaneous or intramuscular injection, oral, intravenous) and frequency of administration differ according to the medication with some involving day case treatment. Secondary care follow-up monitoring in MS outpatient clinics is often required. Serious adverse reactions include progressive multifocal leukoencephalopathy (PML), cardiac and liver toxicity, secondary autoimmune diseases, and malignancy[5].

The European Medicines Agency (EMA) is reviewing the safety of alemtuzumab following reports of immune-mediated conditions and problems with the heart and blood vessels, including fatal cases (https://www.ema.europa.eu/en/medicines/human/referrals/lemtrada). This has led to restrictions in prescribing where alemtuzumab should only be provided to adults with relapsing-remitting multiple sclerosis that is highly active despite treatment with at least two disease-modifying therapies or where other disease-modifying therapies cannot be used.

Outcome measures

DMT aims to reduce the occurrence of relapse and to halt disability progression. NEDA (no evidence of disease activity) is a composite outcome encompassing; absence of clinical relapse, disability progression and radiological disease activity on magnetic resonance imaging (MRI).

Disability in MS is measured using the Kurtzke's expanded disability status scale (EDSS). The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent increasing levels of disability. Scoring is based on an examination by a neurologist covering eight functional systems (neuronal networks) as below:

- pyramidal – muscle weakness or difficulty moving limbs
- cerebellar – ataxia, loss of balance, coordination or tremor
- brainstem – problems with speech, swallowing and eye movement
- sensory – numbness or loss of sensation
- bowel and bladder function
- visual function - problems with sight
- cerebral functions - problems with thinking and memory
- other

EDSS scores 1.0 to 4.0 refer to people with MS who are able to walk without any aid. After 4.0 the EDSS is predominantly focused on changes in mobility with wheelchair use beginning at EDSS 7.0[7].

In trials, disability progression is defined as a specific change in score at a particular time point, and is relative to the baseline score. For example, disability progression may be represented by an increase of at least 0.5 points in patients with high disability score (EDSS>6.0), or an increase of at least 1.0 for patients with moderate levels of disability (EDSS 2.0 to 6.0), on two evaluations six months apart after at least a year of treatment[8]. This may also be referred to as disease progression. There are concerns about the reproducibility and inter-rater agreement of EDSS assessment and the validity of pooling EDSS assessments conducted in different contexts[9].

Health technology description

Autologous haematopoietic stem cell transplantation (AHSCT) is an inpatient therapeutic medical procedure in which stem cells are taken from patients and re-infused after high dose cytotoxic therapy. The aim of AHSCT is to reset the immune system by eradicating the self-reactive immune cells responsible for the disease and regenerating a naïve and self-tolerant immune system from haematopoietic precursors[4].

In a small audit in England (n=54) the median inpatient stay was 22 days (range 17-81)[10]. Treatment protocols vary but the treatment typically involves the following phases[11, 12]:

1. Mobilisation of stem cells – patients are given a combination of drugs to encourage blood cells to migrate from the bone marrow into the blood stream where they can be harvested. This phase involves infusion of a chemotherapy drug (cyclophosphamide) and injections of a synthetic form of a natural growth factor called G-CSF (granulocyte-colony stimulating factor).

2. Harvesting of stem cells from circulating blood - typically around 10 days after mobilisation treatment. The stem cells are frozen for later use.

3. Conditioning chemotherapy - this second round of chemotherapy either eradicates (myeloablative or high intensity chemotherapy) or partially eliminates (non-myeloablative chemotherapy) the bone marrow and immune system, destroying the cells involved in MS disease activity. This stage usually takes several days. Recent procedures have tended to use the less aggressive low or intermediate intensity chemotherapy methods. Outcomes from the procedure are likely to be influenced by the intensity of conditioning chemotherapy. None of the chemotherapy drugs used in the AHSCT procedure (for any indication) have marketing authorisations covering such use[13].

4. Transplantation – the stored stem cells are thawed and returned to the patient's blood by infusion. In a process known as engraftment, the stem cells make their way to the bone marrow and start producing new blood and immune cells within 10 to 30 days. Until the transplanted stem cells start producing these blood and immune cells the patient effectively no functioning immune system.

5. Supportive care – during the period when the immune system and bone marrow are unable to produce sufficient cells to maintain blood counts and immunity, supportive care and close monitoring are required. This may include use of antibiotics (prophylactic and therapeutic), blood transfusions and growth factors.

Epidemiology

The annual incidence rate of MS in Scotland is 8.64 cases per 100,000 people. Across Scotland, incidence rates vary, ranging from 6.24 cases per 100,000 people in NHS Borders to 17.36 cases per 100,000 people in NHS Orkney, which is consistent with the association between geographical latitude and incidence rates[14].

In 2017, the Scottish Public Health Observatory estimated there were 7,200 females and 2,940 males in Scotland who have or probably have MS. During 2017, there were 425 new diagnoses of MS and 171 deaths occurred with underlying MS recorded as the cause[2].

The European Group for Blood and Marrow Transplantation (EBMT) registry has recorded 1,271 autologous haematopoietic stem cell transplants for MS up to September 2018. This encompasses data from >600 centres in Europe and other regions including Australia, Canada and Brazil, and includes all MS types[6, 15].

In NHSScotland, during the period 2009 to 2018, six AHSCT procedures were recorded in patients who had a diagnosis of multiple sclerosis (R Munro, Principal Information Analyst, ISD Scotland. Personal Communication, 18 June 2019).

Data collated by the Scottish HSCT network indicates that at least 32 patients from Scotland have travelled abroad for AHSCT (see patient group submission, appendix 1).

As of May 2016, 41 patients had received AHSCT for MS within NHS England transplant centres in Sheffield and London[4]. Recent data collated by the MS Society indicate that 214 MS patients have now received AHSCT in NHS England since 2002 (see patient group submission, appendix 1).

Clinical effectiveness

Guidelines

Guidelines from the European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party and the Joint Accreditation Committee of the International Society for Cellular Therapy and EBMT (JACIE) were published in 2019[16]. The guidelines recommend that:

> *AHSCT should be offered to patients with RRMS with high clinical and MRI inflammatory disease activity (at least 2 clinical relapses, or one clinical relapse with*

Gd enhancing or new T2 MRI lesions at a separate time point, in the previous 12 months) despite the use of one or more lines of approved DMTs.

AHSCT should be delivered in transplant units that provide high quality care and are accredited by JACIE or equivalent organisations.

Units should be experienced with close collaboration between HSCT and neurology specialists throughout the patient journey including medium- and long-term follow up.

A statement developed by NHS England's Neuroscience Clinical Reference Group in September 2018 states:

Autologous haematopoietic stem cell treatment for autoimmunity is commissioned at specialised centres and is currently being offered to some people with MS in some parts of the UK. But there is not yet an adequately controlled trial of its efficacy relative to other potent therapies. We recommend that it is made available equitably to all people with MS, but we propose that it should only be considered for people with relapsing disease (not progressive) who have failed high-activity licensed disease-modifying therapies, and are prepared to accept the significant risks of the procedure and are eligible under European Group for Blood and Marrow Transplantation (EBMT) guidelines. We recommend that this treatment is offered only by units with expertise both in the management of aggressive multiple sclerosis and the use of autologous haematopoietic stem treatment.

An MS treatment algorithm illustrating the positioning of AHSCT in England has been developed and is available at: https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/

An international conference on cell-based therapies for multiple sclerosis in 2015 developed the following consensus statement regarding immunoablation followed by autologous haematopoietic stem cell transplantation (I/AHSCT):[17]

In aggregate, the available evidence suggests I/AHSCT has substantial and sustained efficacy in suppressing inflammatory disease activity in multiple sclerosis. However, at present, it remains uncertain where the benefit-risk-cost profile of I/AHSCT places it in the treatment for RRMS relative to other available highly effective DMTs.

Randomised controlled trials

Two randomised controlled trials (RCTs) in patients with MS were identified. The first, conducted between 2004 and 2009, compared the effect of AHSCT with mitoxantrone treatment on disease activity as measured by MRI[18]. In this small study (n=21) only two patients with RRMS had AHSCT so this trial is not directly relevant to the research question for this evidence synthesis. In addition, mitoxantrone is not licensed for MS in the UK and is rarely used for this indication.

The most recent RCT (MIST), described as a preliminary study, randomised patients with RRMS which remained highly active despite treatment with DMTs, to receive either low intensity non-myeloablative AHSCT (n= 55) or DMT (n=55) of higher efficacy or a different class than they were taking prior to enrolment[8]. The study was conducted between 2005 and 2016 across four centres, in US, Sweden, Brazil and England. In 2016, the principal investigator of this study received an FDA letter of warning around issues of trial conduct which were subsequently resolved[19]. Details of the patient group and the interventions in the MIST trial are outlined in Table 1.

Table 1: Parameters of the MIST trial[8]

Study inclusion criteria	DMT intervention	AHSCT intervention	Excluded patients
RRMS ≥2 clinical relapses or 1 relapse and MRI-gadolinium enhancing lesions at separate times within previous 12 months despite DMT. EDSS 2.0 to 6.0	Approved DMT of higher efficacy or different class from their current therapy. The most frequently received DMTs were natalizumab and dimethyl fumerate. Could additionally receive immune-modulating or immunosuppressive drugs.	Use of DMT was discontinued (variable drug-specific washout periods observed). Mobilisation – cyclophosphamide, subcutaneous filgrastim. Non-myeloablative conditioning, cyclophosphamide and antithymocyte globulin. Antimicrobials.	Primary or secondary progressive MS. Prior treatment with alemtuzumab or mitoxantrone. Use of natalizumab within the prior 6 months. Recent treatment with Fingolimod.

Although conducted in patients with highly active RRMS despite treatment with DMTs, the study excludes contemporary high-efficacy DMTs meaning that benefit/harm profiles comparing AHSCT with these treatments were not assessed. Ocrelizumab was excluded as it was not licensed at the time of the trial and alemtuzumab was excluded due to potential risk of complications that might prevent cross-over from the DMT group to the AHSCT group - which was permitted in this trial after one year of treatment for patients with disability progression. Natalizumab was noted among prior therapies for seven patients in the AHSCT group and 11 patients in the DMT group.

A comparison of DMT in the MIST trial with current treatment in Scotland is provided in Table 2.

Table 2: Profile of high-efficacy DMT use in Scotland compared with MIST trial

DMT	Patient numbers in Scotland April 2019^	Patient numbers – RCT prior therapies AHSCT arm/DMT arm
Fingolomod	1,704	6/3[α]
Cladribine	between 120 and 130	Nil
Natalizumab	between 457 and 465	7/11[α]
Alemtuzumab*	203	Not applicable
Ocrelizumab	between 14 and 22	Not applicable

* Ongoing safety review of alemtuzumab will limit prescribing.

^ K Park, MS Society, Personal Communication, 22 July 2019

[α] Patients with fingolomod use in previous 3 months were excluded as were patients with natalizumab use within 6 months (see table 1)

Of the 55 patients randomised to the DMT arm, four were lost to follow-up after transferring to another centre for AHSCT, and 31 crossed over after at least one year of the DMT treatment to receive AHSCT. The impact on the study outcomes of the expectations of patients who may wish to access the novel therapy is unclear, but may introduce risk of bias.

Of the 55 patients randomised to the AHSCT arm, three did not receive the intervention, with two cases due to the diagnosis of secondary progressive disease and one due to recurrent infections.

The primary outcome measure was time to disease progression defined as an increase in EDSS score (due to MS) of at least one point on two evaluations six months apart after at least one year of treatment. EDSS score was assessed by a neurologist blinded to treatment allocation. Patients were instructed not to disclose treatment allocation, and patients in both treatment groups wore a wig to mask the effect of AHSCT on hair loss.

Patients were followed up at six months and one year (n=98), then annually for up to five years (n=23). There were no deaths during the study.

Mean follow up was 2.8 years (median 24 months, interquartile range (IQR) 12 to 48 months). In the AHSCT group three patients experienced disease progression, whilst for the DMT group progression was experienced by 34 patients. In the DMT group, median time to progression (the point at which 50% of participants will have experienced progression) was 24 months. For the AHSCT group, the number of events was too low to allow calculation of

median time. Compared with DMT, AHSCT prolonged time to disease progression, hazard ratio (HR) 0.07 (95% confidence interval (CI) 0.02 to 0.24, p<0.001).

In the AHSCT group, mean EDSS score improved from baseline (3.38) to one year (2.36) (mean change -1.02 points), whilst for the DMT group the mean score worsened from baseline (3.31) to one year (3.98) (mean change +0.67 points). The between-group difference in change in EDSS score was -1.70 (95% CI -2.03 to -1.29, p<0.001).

Relapse rates were assessed in the study, but these may be subject to bias owing to lack of blinding of assessors to treatment assignment. Relapses were defined as neurologic symptoms lasting more than 24 hours, not associated with infection, fever or heat intolerance, and deemed to require corticosteroids. In the first year, 69% of patients in the DMT group experienced a relapse compared with 2% of patients in the AHSCT group. The between-group difference was 78% (95% CI 64% to 88%, p<0.001).

Pre-specified secondary endpoints included the neurologic rating scale (NRS). This neurological examination was conducted by a neurologist blinded to treatment allocation and comprises a score ranging from 0 to 100, where 0 reflects the worst outcome and 10 represents the minimum clinically important difference. At baseline, the mean NRS score was 79.5 (standard deviation (SD) 10.2) for the AHSCT group and at one year this improved to 88.3 (SD 9.15), whilst for the DMT group the score worsened from 81.1 (SD10.9) to 79.5 (SD 11.8). The between-group difference in change in score was 11.2 (95% CI 8.08 to 14.29, p=0.001).

Additional secondary outcomes in the MIST trial were as follows, with the findings outlined in Table 3:

- MRI T2-weighted lesion volume – lesions marked by unblinded observer, and an experienced reader masked to treatment assignment reviewed a random selection of MRI scans for accuracy
- Short form 36 (SF36) – self-reported quality of life measure
- Timed 25-foot walk test – 20% change is clinically meaningful
- 9-Hole Peg Test – a measure of arm function, 20% change is clinically meaningful
- Paced auditory serial addition test (PASAT) – result is % correct answers from 60 questions, clinically meaningful difference not known.

At one year, lesion volume had increased in the DMT group, whilst it had decreased in the AHSCT group. Quality of life score were significantly improved in the AHSCT group compared with the DMT group. The timed 25-foot walk test, 9-Hole Peg Test and PASAT were combined in a Multiple Sclerosis Functional Composite (MSFC) score, where an increasing score represents improvement. At one year, the between group difference in change in MSFC score was 0.51 (95% CI 0.28 to 0.72, p< 0.001) favouring the AHSCT group. Scores may be biased by the impossibility of blinding of patients to treatment allocation.

Table 3: MIST trial secondary outcomes[8]

	DMT		AHSCT		Between-group difference in change from baseline (95% CI)
	Baseline Mean (SD)	1 yr Mean (SD)	Baseline Mean (SD)	1 yr Mean (SD)	
MRI lesion volume (%)	100 [12.54 cm^3]	134.3 (45.6)	100 [16.2 cm^3]	68.3 (20.7)	-66 (-70.6 to -61.3) p<0.001
SF36 (total score)	49.5 (18.0)	46.1 (22.5)	50.5 (20.1)	70.3 (21.3)	23 (17.6 to 28.9) p<0.001
Timed 25 foot walk (seconds)	5.6 (1.7)	8.0 (6.2)	6.5 (3.16)	6.0 (4.5)	-2.85 (-3.92 to -1.77) p<0.001
9-Hole Peg Test (seconds)	24.7 (6.3)	25.6 (8.2)	30.8 (23.2)	24.0 (9.5)	-8.03 (-11.3 to -4.76) p<0.001
PASAT (%)	65.2 (21.5)	75.4 (22.5)	67.4 (20.9)	77.8 (21.1)	0.22 (-72.4 to 72.9) p=0.61

The MIST trial report focused on adverse events for the AHSCT procedure. No deaths or complications with life-threatening consequences or requiring urgent intervention were recorded during the trial. Severe or medically significant transplant-related toxicities experienced by more than one patient were culture-negative febrile neutropenia (13 patients), hypophosphataemia (17 patients), hypokalaemia (13 patients), hyperglycaemia (five patients), hypertension (three patients), elevated liver transaminases (five patients). The following post-transplantation infections occurred; 16 upper respiratory tract infections, six urinary tract infections, two *C.difficule* diarrhoea cases, and seven dermatomal varicella zoster reactivations.

For the DMT group the following infections were noted; 15 upper respiratory tract infections, eight urinary tract infections and two varicella zoster reactivations.

The overall rate of infection per patient per year was 0.19 in the AHSCT group and 0.23 in the DMT group. It is unclear how this was calculated or if this difference was statistically or clinically significant. The study report notes that there were no early or late fungal, *Pneumocystis jirovecii*, cytomegalovirus, Epstein-Barr, or JC (John Cunningham) virus infections in either group.

Post hoc analysis was undertaken to explore the comparison between participants receiving AHSCT, any DMT, and the findings for the 19 evaluable patients who received natalizumab - which was the only high-efficacy DMT included in the MIST trial. Table 4 summarises this analysis. Patients receiving natalizumab had lower rates of disease progression than the overall DMT group, although confidence intervals were wide and only provided in graphical format in the study supplementary materials. Study authors did not comment on the comparison between patients receiving AHSCT and those receiving natalizumab, although it appears that AHSCT outcomes were superior.

Table 4: MIST post hoc subgroup analysis of disease progression in patients receiving natalizumab[8]

Estimated proportion of patients with disease progression (worsening on EDSS) **Mean follow up 2.8 years**			
	AHSCT (95% CI)	**DMT (95% CI)**	**Natalizumab* (95% CI)**
1 year	1.92 % (0.27% to 12.9%)	24.5 % (14.7% to 39.1%)	5.3%
2 year	1.92 % (0.27% to 12.9%)	54.5 % (40.7% to 69.4%)	24.3%
3 year	5.19% (1.26% to 20.1%)	62.5 % (48.3% to 76.7%)	30.5%
4 year	9.71% (3.0% to 28.8%)	71.2 % (56.8% to 84.2%)	46.0%
5 year	9.71% (3.0% to 28.8%)	75.3% (60.4% to 87.8%)	67.6%
*confidence intervals were wide and only provided in graphical form in the study report			

Ongoing clinical trials

Five ongoing trials were identified with details outlined in Table 5. A protocol for a Cochrane systematic review was also identified[20].

Table 5: Ongoing clinical trials

Trial	Sites Identifier	Number of patients	Primary completion due
Randomized Autologous Haematopoietic Stem Cell Transplantation Versus Alemtuzumab for Patients With Relapsing Remitting Multiple Sclerosis (RAM-MS)	Denmark, Sweden, Norway NCT03477500	100	2022
Maximizing Outcome of Multiple Sclerosis Transplantation (MOST) Comparing two different conditioning regimens for autologous haematopoietic stem cell transplantation	US NCT03342638	200	2023
RCT Comparing Autologous Haematopoietic Stem Cell Transplantation Versus Alemtuzumab/Ocrelizumab in MS (STAR-MS)[21]	UK	198	2024
Best available therapy versus autologous haematopoietic stem cell transplantation for MS (BEAT-MS) [AHSCT versus best available approved treatment]	US (NIH) NCT04047628	156	2025
AHSCT versus ocrelizumab or alemtuzumab (COAST)	Germany	Not known	Not known
No evidence of disease activity in AHSCT versus best available therapy in aggressive forms of MS (NET-MS)	Italy	Not known	Not known

Observational studies

Systematic review

A systematic review and meta-analysis of single arm observational studies was identified[9]. Fifteen studies were included (one of which was the treatment arm of an RCT) across the period 1995 to 2016. Ten studies were prospective and five were retrospective. Data for 764 transplanted patients were analysed. Seven studies used an intermediate intensity regimen (BEAM: BCNU, etoposide, Ara-C and melphalan). Median EDSS at baseline was 5.6 (compared with 3.0 in the MIST RCT population). Only two studies in the meta-analysis included solely patients with RRMS. Subgroup analyses were presented, which compared the findings of the seven studies with ≥44% of patients with RRMS, with findings from the remaining eight studies where patients with RRMS made up <44% of the study population. Results from this meta-analysis are shown in Table 6.

Overall transplant-related mortality (TRM) was 2.1%. For the seven studies which had ≥44% RRMS patients, the mortality rate was lower at 1.0% (p value for the interaction between MS type and TRM =0.004). There was no additional mortality during the first year after transplant.

TRM was lower for seven studies conducted post-2005 (0.3%, 95% CI 0.0% to 2.0%) when compared with eight studies conducted pre-2005 (3.6%, 95%CI 2.2% to 6.0%), p value for the interaction =0.014. There was no statistically significant association of TRM with regimen intensity (high, intermediate, low), although TRM was zero among 119 patients treated with low-intensity regimens. Expert opinion suggests that the decline in TRM rate over time is due to decreased use of high-intensity conditioning regimens, improved patient selection and improvements in supportive care[22].

Study baseline EDSS ≤5.5 was associated with lower TRM when compared with EDSS >5.5, although only four studies had baseline EDSS≤5.5. The authors concluded that AHSCT has the most favourable risk-benefit profile in patients with RRMS who do not have a high level of disability.

Two-year rate of disability progression was 17.1% in the overall cohort, but was significantly lower at 7.8% when only the seven studies with ≥44% RRMS patients were analysed (p value for interaction =0.004). There was substantial heterogeneity in these analyses as indicated by I^2 statistic values greater than 50%. The five-year rate of disability progression for the overall cohort was 23.3%.

Five studies in the analysis (274 patients) provided information on NEDA. At two years, the proportion of patients with NEDA was 83.4%, and at five years it was 67%.

Table 6: Meta-analysis findings[9]

Outcome	Full review	Studies ≥44% RRMS 7 studies (n=414)	Studies <44% RRMS 8 studies (n=350)
Transplant related mortality (100 days)	15 studies (n=764) 2.1% (95%CI 1.3% to 3.4%) I^2 = 37%	1.0% (95%CI 0.4% to 2.6%)	3.4% (95%CI 1.9% to 6.0%)
2 year rate of disability progression	15 studies (n=764) 17.1% (95%CI 9.7% to 24.5%) I^2 = 83.3%	7.8% (95%CI 1.3% to 14.2%)	24.8% (95%CI 16.7% to 32.9%)
5 year rate of disability progression	15 studies (n=764) 23.3% (95%CI 16.3 to 31.8) I^2 = 69%		
2 year NEDA proportion (range)	5 studies (n=274) 83.4% (70%-92%)		
5 year NEDA Proportion (range)	4 studies (n=233) 67% (59%-70%)		

Primary studies

Six observational studies - published since the systematic review[9] - were identified. One of these was a comparative study but was excluded from this report since the comparator group included patients with mild or no disease activity[23]. One study was an update of an analysis of patients included in the systematic review[24]. A further study[3] was excluded on the basis that it focused solely on fatigue, and the main findings were encompassed within the systematic review.

The remaining three uncontrolled observational studies published since the systematic review are described here. All three studies compare AHSCT outcomes for patients with RRMS versus patients with progressive forms of MS, with findings suggesting that patients with RRMS have the more favourable outcomes following treatment with AHSCT.

The first prospective study is a single-arm phase II clinical trial of AHSCT in patients with active, treatment refractory MS[25]. This small study, conducted in Australia, included 20 patients with RRMS and 15 patients with SPMS. Patients had a median EDSS at baseline of 6.0 (range 2.0 to 7.0) and clinical or MRI activity despite treatment with DMTs including natalizumab - which 66% of participants had been exposed to. The patients with RRMS had failed to respond to a median of four DMTs. Transplant procedures were performed between 2010 and 2016. There was no treatment-related mortality. Median follow-up was 36 months (range 12 to 66). The primary outcome was event-free survival (EFS) - no relapses, no new or expanding lesions on MRI and no EDSS progression.

In patients with RRMS, estimated EFS was 90% (95% CI 66% to 97%) at one year and 70% (95% CI 41% to 87%) at years two and three, and this was not significantly different to the SPMS cohort. In the RRMS cohort, EDSS progression-free survival was 95% (95% CI 72% to 99%) at one year and 88% (95% CI 60% to 97%) at years two and three, which was statistically superior to the rates in the SPMS cohort (p=0.04). In the RRMS cohort, at last follow-up assessment, EDSS significantly improved in 12 patients, was stable in six patients and declined in two patients. Only one patient in the SPMS cohort had an improvement in EDSS.

The multiple sclerosis quality of life instrument (MSQoL-54) physical and mental health scores were significantly higher compared with baseline at each time point following AHSCT in the RRMS cohort. Patients experienced expected complications of high-dose chemotherapy including mucositis, nausea and alopecia. Twenty-two of 35 patients experienced serum sickness associated with the antithymocyte globulin. Serious adverse events recorded within 100 days of the procedure were bacteraemia (three), viral infection (four) central venous catheter thrombosis (two), secondary autoimmune disorder (one), Mallory-Weiss tear (two), acute kidney injury (one), parenteral nutrition (two).

In the second prospective observational study, conducted in Spain, efficacy data were available for 22 patients with RRMS who received AHSCT and were followed up for more

than two years (mean follow-up 5.9 years, SD 3.7)[26]. Mean baseline EDSS was 5.0 (SD 1.3) and at last follow up was 3.4 (SD 1.2) - indicating a sustained improvement in EDSS over time. None of the RRMS patients experienced progression of disability. Six patients (27.2%) experienced at least one post-transplant relapse.

Adverse event data were recorded for an overall study population of 38 patients (28 RRMS, 10 secondary progressive MS). There were no transplant-related deaths. Across the cohort, 63% of patients experienced gut toxicities, 47% skin toxicity, 45% had mucositis and 39% of patients had liver toxicity. The most serious toxicities (WHO toxicity grade 3 and 4) were gut toxicities (2), skin toxicities (2) and hepatic events (4). Neurological toxicity was experienced by 13% of patients and coagulation toxicity by 11%.

The third observational study was a retrospective study that examined outcomes data from US and European registries on AHSCTs conducted between 1995 and 2006, at 25 centres across 13 countries[27]. Data are likely to include some of the procedures incorporated in aforementioned systematic review and meta-analysis. Information on 281 of 493 (57%) eligible transplants was included. The risk of bias from this low reporting rate is unclear. The main reason for non-inclusion was that centres performing small numbers of transplants did not wish to participate in the study.

The median EDSS score was 6.5 (range 1.5 to 9.0) and 46/281 (16.4%) patients had RRMS. The majority of patients had SPMS 186/281 (66.2%), likely reflecting that early AHSCT procedures were predominantly offered to patients with longstanding severe progressive MS[15, 17]. Median follow-up was 6.6 years (range 0.2 to 16 years).

The primary outcome was progression-free survival. Data for this outcome were available for 239/281 patients (85.1%). Across all evaluable patients, 5-year progression-free survival was 46% (95%CI 42% to 54%). In the group of patients with RRMS (n=53), progression-free survival was 73% (95%CI 57% to 88%). It is unclear from the study report, but the RRMS group is likely to have included some patients with disease described as progressive relapsing disease.

Eight deaths within 100 days of transplantation were reported (2.8%, 95% CI 1.0% to 4.9%). One death was in a patient with a relapsing form of MS (1/63 = 1.6%), with the remaining seven in patients with progressive MS. Causes of death within 100 days of transplantation were infection (two patients), accident (one patient), veno-occlusive disease (one patient), haemorrhage (one patient) Epstein-Barr virus lympho-proliferative disorder (one patient), with cause not reported for two patients.

Late adverse events included autoimmune thyroid disease (eight), autoimmune thrombocytopenia (three), acquired haemophilia (two), Crohn's disease (one), giving a rate of 5% across the cohort. There were nine (3.2%) new malignancies, three of which were myodysplastic syndrome.

Safety

None of the conditioning chemotherapy drugs used in the AHSCT procedure have marketing authorisations covering such use[13].

Adverse events data for AHSCT from the individual studies are outlined in the clinical effectiveness section above and include effects associated with immune suppression such as febrile neutropenia, respiratory and urinary tract infections and virus reactivations, as well as late effects, such as thyroiditis.

Although it is not possible to provide reliable estimates for the frequency of events, a range of safety issues associated with AHSCT for MS include: [22, 28]

- Alopecia – which occurs in almost all cases
- Fever, sepsis, urinary tract infections and viral reactivations
- Amenorrhoea and the risk of permanent infertility for females and males
- Neurological toxicity
- Liver toxicity
- Epstein–Barr virus post-transplant lymphoproliferative disorder
- Secondary autoimmune diseases
- Malignancies

The impact of the underlying MS symptoms (such as mobility problems) and the contribution of previous treatments on risk of complications from AHSCT is unclear.

In a small audit carried out in England (n=54) and published in form abstract only, 22% of patients required re-admission following the AHSCT procedure and had a median length of stay of 9 days (range 3 to 119 days)[10].

Patient and social aspects

A literature search for patient issues was undertaken. No published studies specifically examining the experiences of patients undergoing AHSCT for MS were identified. A position statement from the EBMT Autoimmune Diseases Working Party (ADWP), the EBMT Nurses Group, the EBMT Patient, Family and Donor Committee and the Joint Accreditation Committee of ISCT and EBMT (JACIE) provided guidance for patients considering HSCT for autoimmune disease[29].

Two patient organisation submissions were received by SHTG. The first, jointly submitted by the Scottish HSCT Network and the MS Society Scotland is presented in Appendix 1. The submission incorporated data from surveys conducted by the HSCT Network through their forum on Facebook. The submission includes a statement of support from the charity A.I.M.S (Auto Immune and Multiple Sclerosis).

Key points directly drawn from their submission include:

- Scotland has the highest prevalence per capita of MS in the UK. MS has devastating consequences for patients, family and carers. MS greatly impacts on the workforce and economy.
- Current treatment options for MS are not effective for all patients and DMT's have serious side effects and risks. AHSCT has been proven to halt disease progression and optimal treatment results are obtained when given before disability accumulates.
- Autologous HSCT is already provided on NHSScotland for cancer patients. Patients with other auto-immune conditions can already be referred and funded for AHSCT via reimbursement from NHS England.
- AHSCT is a highly effective treatment for some MS patients i.e. RRMS patients not responding to 3rd line DMT treatment. However, HSCT is an invasive treatment with risks and patients need to be informed of the risks and possible complications during treatment and recovery.
- MS patients in Scotland want access to AHSCT in Scotland under NHS Scotland. They want the support of NHS Scotland clinicians, family and friends. There is a recognised need for NHS staff to provide accurate and consistent information on AHSCT and aftercare.

A second patient group submission, from the MS Trust, is presented in Appendix 2. The submission include a description of the level of demand which the MS Trust experiences for information on HSCT, and draws upon on interviews with two recipients of AHSCT.

Key points directly drawn from the submission include:

- MS is a complex and unpredictable condition which has an impact on all aspects of life; early proactive treatment is essential to prevent future disability.
- Continuing to have relapses and acquire disability despite switching to increasingly more effective DMTs takes a heavy toll on psychological and physical health, and quality of life, employment and financial status, not only for the person with MS but also for their family who often act as informal carers.

- AHSCT is a highly effective treatment for RRMS, with the ability to very significantly reduce the rate of relapses, slow down progression and, in some cases, reverse disability, giving people hope for a better quality of life in the long term.
- As a one-off therapy, AHSCT reduces the burden of treatment and monitoring for both people with MS, their families and the NHS compared with DMTs. However, the demands of the treatment may not suit everyone; as with the DMTs, an individual and their MS team will need to consider the risks and benefits of AHSCT before deciding whether it is the right treatment for them.
- Extensive clinical evidence supports the use of AHSCT; internationally, it is an established treatment for people with highly active RRMS and it is important that people living in Scotland are not denied access to this innovative treatment.

Organisational issues

Expert reviews note that delivery of AHSCT requires close collaboration between transplant haematologists and MS neurologists in patient selection, clinical management, rehabilitation and follow up[11]. A multidisciplinary team approach is required that involves fertility services and allied healthcare professionals, as well as haematology and neurology experts[6].

Budget impact analysis

The literature search did not identify any relevant and peer-reviewed studies investigating the cost effectiveness of AHSCT in patients with RRMS. It was not feasible for SHTG to undertake a de-novo cost effectiveness analysis owing to widespread limitations with the quality of evidence available to populate the analysis. Limitations include the absence of RCTs comparing AHSCT with current high-efficacy DMTs, limited outcomes data particularly long term endpoints, and wide variation in costing estimates contingent on local treatment protocols. However, given that AHSCT could potentially lead to a reduction in long-term use of DMTs in treatment refractory patients, a budget impact analysis was conducted.

The budget impact analysis is informed by epidemiology and cost data from several different sources. The total MS population in Scotland was calculated by applying an annual incidence rate of 13 new cases per 100,000 people (based on MS Society data – Appendix 1) to reported prevalence in Scotland for 2016 (MS Society data), and an annual mortality rate of 0.2%. In the absence of more recent data, these total numbers are expected to be an underestimate. Reported proportions of MS patients with RRMS varied between 65% and 85%. The number of patients eligible for AHSCT as rescue therapy was estimated by applying further reductions to the total number of RRMS patients, based on data obtained from previous SMC appraisals for ocrelizumab, cladribine and alemtuzumab. The assumptions made in deriving eligible patient numbers are summarised in Table 7.

Table 7: Budget impact analysis assumptions used in deriving eligible patient numbers

	Base case	Sensitivity analysis	Source
(1) Patients with RRMS	85% of MS prevalence	65% of MS prevalence	MS Society; SMC appraisals
(2) Highly active RRMS on DMTs	46% of (1)		FoI hospital trusts UK 2017
(3) Highly active RRMS failing 2nd line therapy	18% of (2)		SMC appraisals
(4) Patients with rapidly evolving severe (RES) MS	25% of (1)		SMC appraisals
(5) RES MS failing 2nd line therapy	40% of (4)	20% of (4)	Assumption
(6) AHSCT eligible	(3) + (5)		
(7) Treated with AHSCT	2% in year 1 rising to 10% in year 5	Up to 100% uptake	Assumption

The budget impact was based on two different estimates for the cost of performing AHSCT. The average cost of all AHSCT in Scotland, based on 156 cases in 2017/18, was £19,704 per procedure (A Shito, Information Analyst, ISD Scotland. Personal Communication, 19 July 2019). This is lower than the average cost of £28,200 per patient for AHSCT procedures (specifically for MS patients) completed at the specialist centre in London. Hence, results are presented based on both cost estimates. Based on the lower procedure cost, the gross cost of AHSCT is expected to be £732K in year 1 rising to £4.01 million in year 5. The gross cost of AHSCT at the higher procedure cost, is expected to be £1.04 million in year 1 rising to £5.70 million in year 5.

The budget impact analysis also incorporates costs associated with post-AHSCT hospital readmission and maintenance on DMTs for patients with AHSCT treatment failure. The cost of displaced medicines was calculated using a treatment basket approach based on market share distribution of DMTs obtained from SMC submissions. Data are presented in Table 8.

After taking into account the savings realised from reduced DMT usage, the net budget impact of AHSCT at the lower procedural cost per patient, is expected to be £358K in year 1 rising to £2.12 million in year 5. The net budget impact of AHSCT at the higher procedural

cost per patient, is expected to be £666,045 in year 1 (based on 37 patients treated) rising to £3.81 million in year 5 (based on 203 patients treated).

Table 8: Budget impact analysis findings

Base case analysis	Year 1	Year 2	Year 3	Year 4	Year 5
Patient numbers					
Net patients with RRMS	10193	10791	11389	11987	12586
AHSCT eligible	1857	1929	1999	2048	2034
% treated with AHSCT	2%	2%	3%	6%	10%
Patients treated with AHSCT	37	39	60	123	203
Costing					
Gross cost AHSCT (ISD)	£731,677	£759,991	£1,181,606	£2,421,156	£4,007,879
Gross cost AHSCT (London)	£1,039,737	£1,079,970	£1,679,100	£3,440,539	£5,695,321
Additional costs	£114,762	£119,203	£185,332	£379,753	£628,627
Net Cost AHSCT (ISD estimate)	£846,439	£879,193	£1,366,939	£2,800,909	£4,636,505
Net Cost AHSCT (London estimate)	£1,154,499	£1,199,173	£1,864,432	£3,820,292	£6,323,947
Displaced medicines (Savings)	£488,454	£501,711	£768,270	£1,521,120	£2,512,827
NET budget impact (ISD)	**£357,986**	**£377,482**	**£598,669**	**£1,279,790**	**£2,123,678**

NET cost per patient	***£9,641***	***£9,787***	***£9,983***	***£10,415***	***£10,441***
NET budget impact (London)	**£666,045**	**£697,462**	**£1,096,162**	**£2,299,172**	**£3,811,120**
NET cost per patient	**£17,937**	**£18,083**	**£18,279**	**£18,711**	**£18,737**

It is worth noting some of the key areas of uncertainty with the analysis:

- There is some uncertainty regarding overall RRMS prevalence and proportion of rapidly evolving severe (RES) MS patients eligible for rescue therapy. More up to date information on epidemiology is desirable to estimate the size of the AHSCT eligible patient sub group. Decreasing the proportion of MS patients with RRMS to 65% and proportion of RES MS patients eligible for rescue therapy down to 20% results in a lower budget impact as illustrated in Table 9.
- The model is most sensitive to the predicted uptake rate which determines the annual number of patients treated with AHSCT. The uptake range of 2%-10% over five years, applied in the base case, is intended to capture the sum of eligible patients who are offered ASHCT if they fail either second or third line therapy. In the sensitivity analysis, a 50% uptake rate leads to a net budget impact of £33.3 million for 1,857 patients treated in year 1 using the London cost.
- Although the analysis attempts to incorporate the additional costs associated with AHSCT (hospital readmissions, best supportive care, and maintenance on DMTs), other elements of resource usage (for example, adverse events, long term disease management) have not been quantified. The overall costs associated with AHSCT may therefore be higher than estimated.
- The savings arising from displaced use of medicines are based on the assumption that all patients treated with AHSCT would have otherwise been on high-efficacy DMTs. This may be an optimistic assumption and in reality, the savings achieved could be lower.

Table 9: Sensitivity analysis findings

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
Base case	**£666,045**	**£697,462**	**£1,096,162**	**£2,299,172**	**£3,811,120**
65% RRMS & 20% RES MS on rescue	£367,848	£385,200	£605,397	£1,269,804	£2,104,834
50% of target population would discontinue DMTs use	£899,679	£937,315	£1,463,190	£3,024,680	£5,009,510
100% of target population discontinues DMTs (i.e. no medicine savings)	£1,133,313	£1,177,168	£1,830,218	£3,750,188	£6,207,900
£60,000 AHSCT cost (peer reviewer)	£1,854,315	£1,931,714	£3,015,133	£6,231,217	£10,320,058
50% uptake in eligible population each year	£16,651,119	£9,378,811	£5,736,347	£3,955,547	£3,001,418

Conclusion

No evidence directly comparing the benefits and risks of AHSCT with current high-efficacy DMTs was identified. One RCT and a collection of observational studies indicate that AHSCT is associated with low rates of disability progression, low relapse rates and improved quality of life. These benefits must be balanced against a transplant related mortality rate in the region of 1%, and the association of the AHSCT procedure with a range of serious adverse effects.

The cost-effectiveness of AHSCT in patients with RRMS not responding sufficiently to high-efficacy DMTs remains uncertain. A budget impact analyses was performed to estimate the net expenditure on AHSCT in Scotland. Owing to the early stage of research on clinical outcomes and variable costs around the use of AHSCT in this population, better quality data are needed to enable meaningful assessment of the cost-effectiveness of this treatment.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

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To propose a topic for SHTG consideration, email shtg.hcis@nhs.net
References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.
A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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The SHTG Committee developed the advice.

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Appendix 1 Patient organisation submission

Joint patient organisation submission from the Scottish HSCT Network and the MS Society Scotland

Healthcare Improvement Scotland | SHTG Advice on health technologies

Patient Organisation Submission Form

Subject of SHTG Assessment

HSCT for Multiple Sclerosis

Name of patient organization

Joint submission from Scottish HSCT Network and MS Society

Health/medical conditions represented

Multiple Sclerosis

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Scottish HSCT Network - www.scottishhsct.net
MS Society Scotland – www.mssociety.org.uk

Date of submission

24th June 2019

1. Tell us about the sources you used to gather information for this submission. (See page 6 of guidance.)

The Scottish HSCT Network in collaboration with the MS Society present this joint submission in support of HSCT as a treatment for MS, in Scotland. Various sources of data have been used to gather information relating to MS and HSCT including;

- Scottish HSCT Network website
- MS Society website
- MS Trust website
- Referenced research papers
- Information from different Freedom of Information (FOI) requests to NHS Scotland

We have also included responses to various surveys (including both closed and free text questions) developed by the Scottish HSCT Network. These surveys were promoted on the Network's online members' forum (on Facebook) and were used to collate patient

and carer led feedback on the reality of living with Multiple Sclerosis (MS) and provide details of the HSCT experience for those living with MS in Scotland (pre and post treatment).

In total we received 75 responses to various questionnaires. These and individual case studies were completed by Network members (of which 5 are referenced). Surveys and case study titles, number of respondents to each and the number of respondents living in Scotland are listed below:

- **Scottish HSCT Experience** (34 responses, all living in Scotland) open to all members.
- **Questionnaire 1 Pre HSCT - Your experience** (36 responses, 33 living in Scotland) open to all members
- **Questionnaire 2 Post HSCT - Your experience** (23 responses, 19 living in Scotland) open to HSCT patients that have undertaken HSCT only
- **Case Study Questionnaire for HSCT Submission** (5 responses, all living in Scotland) open to patients that have undertaken HSCT only

The Scottish HSCT Network holds the only database of HSCT patients living in Scotland. Statistical information from this database is also included within the submission.

Feedback has also been gathered from a cross-section of our members (with differing forms of MS and with differing levels of disability), along with their carers. It gives a very candid account of each members unique experience and highlights the difficulties of living with MS and the struggle to access HSCT for MS in Scotland. This feedback (in the form of personal statements and one to one-conversations with members and carers), demonstrates that MS not only significantly impacts the person living with condition but their family members and other carers also.

Lastly, we have included a statement of support from A.I.M.S. - the only HSCT charity in the UK - Charity no. 1177907.

2. What is the health condition and how does it affect the day-to-day lives of patients and their carers? (See page 7 of guidance.)

MS is a neurological condition that affects the brain and spinal cord, otherwise known as the Central Nervous System (CNS). The body's immune system attacks the protective myelin coating around the nerve fibres resulting in the form of plaques or lesions and over time disability accumulates.

There are nearly 700 new cases of MS diagnosed in Scotland each year. For every man diagnosed there are 2.3 women. MS can affect all ages (from under 10's to over 90's. Most men are diagnosed in their 50's and women in their 40's.

Source: MS Society website (MS In the UK)

The estimated number of people with MS around the UK is:

Wales (4,300) or 138 per 100,000

England (90,500) or 164 per 100,000

Northern Ireland (3,200) or 175 per 100,000

Scotland (11,300) or 209 per 100,000
(Source: MS Trust Website)

Main types of MS

Relapsing Remitting MS (RRMS) - Around 85% diagnosed are this type.

Secondary Progressive MS (SPMS) - This often follows on from RRMS.

Primary Progressive MS (PPMS) - Around 10 – 15% diagnosed are this type.

As is highlighted above MS is a neurological condition that affects more than 11,000 people in Scotland. Due to the fluctuating and progressive nature of the condition, people are affected differently by symptoms that include fatigue, pain, loss of mobility, visual impairment and cognitive problems.

MS often impacts a person's ability to continue in employment, to provide or care for their families and take part in normal day to day activities. The effects of MS are both physical and emotional; anxiety, depression, experiencing stigma and discrimination are common. Many patients become house bound and have limitations in participating in family- life, socialising or even going on holiday

There is significant financial cost that comes with MS. This can take the form of loss of earnings for the person with MS and for their carer (1). There are costs of buying equipment, mobility aids and carrying out home adaptations and there can be additional costs for help with personal care, cleaning and childcare.

Commonly experienced symptoms include: fatigue, pain, walking and balance issues, dizziness, vision problems, loss of manual dexterity, altered sensation, temperature sensitivity, impaired cognitive function, problems with bladder, bowel and sexual function. This list is not exhaustive but shows how MS can affect day-to-day life.

Case Study 2 - Patient, Grampian
"I am not currently working full time due to MS effects. It affects my confidence due to

walking limitations and overactive bladder function. I have reduced mobility and I have to plan my daily activities and routines due to fatigue"

Case Study 4 - Patient, Greater Glasgow
"… dynamic with wife moved from equal partnership to being 'cared for' ... having your wife cutting up your food in restaurants doesn't really boost your self-confidence / worth / libido etc."

Carer A - Grampian

"A diagnosis of MS is devastating not only to the patient but the family. Suddenly the life you are used to is not the same as there is always the mobility and fatigue of your husband to factor in to plans, which I'm sure sounds selfish but everyday simple activities require planning and consideration and some are just impossible."

Carer B – Forth Valley
"I am on 'alert' to emotionally or practically support at any time. It's harrowing to watch your loved one lose their independence, health, function. Carers become the main liaison for health professionals. It's exhausting navigating the regulation/processes/procedures of social work, benefits, allocation of respite/social care funds. I worry about my family's needs if anything should arise with my own health. Significant impact on my children…emotions of sadness, anger and fear as their situation is possibly different to their friends."

Treatment for MS involves the use of Disease Modifying Therapies (DMT's). These therapies are designed to slow disease progression by reducing inflammation and reduce the number, severity and impact of relapses on people that have them (minimizing the accumulation of disability). DMT's have serious side effects and are contra-indicated for some patients with MS. A patient must have tried and failed a DMT (e.g. Tysabri or Lemtrada) in order to access HSCT on NHS England.

MS is a lifelong, chronic condition and there is currently no cure. Autologous HSCT is a technology that is a third line treatment, featured in the NHS England algorithm that is highly efficacious for people that have not responded to first and second line treatments, which in some patients has halted disease progression and in a number of cases reversed disability (2).

This highly effective treatment offers tremendous hope to patients, in that they can improve their quality of life and maintain their independence for longer.

3. What do patients and carers want from the health technology? (See page 8 of guidance.)

The main reasons patients and carers want to access HSCT for MS in Scotland are -

- **DMT treatment is contra-indicated for some patients**

Some patients with MS are contra-indicated to take the most effective DMT's. In addition, Tysabri and Lemtrada have potentially life threatening risks i.e. progressive multifocal leukoencephalopathy (PML) and haemophagocytic lymphohistocytosis (HLH) respectively (Annex 1).

Case Study 1 - Patient, Forth Valley
" I am now JCV positive... it is becoming more likely that I will become more at risk and have to stop this treatment. The other approved DMT's do not have the same clinical evidence or the same success"

- **Scottish patients with MS want equal access to HSCT treatment**

MS patients want access to different treatment options for their MS, one of which is HSCT. Considerable stress is caused knowing there is a beneficial treatment for MS (HSCT) that they are unable to access. HSCT for MS is available on NHS England but Scottish patients cannot access this.

Case Study 4 – Patient, Greater Glasgow
"It wasn't until the MS nurse offered me a wheelchair as 'you'll be needing it soon' and I said, 'to-hell-with-that, I'm-off-to-Moscow!!!' Then they started seriously engaging in discussion about HSCT with me - my neurologist eventually suggested that there was no reason why the treatment couldn't be provided in Glasgow, he believed that my history/symptoms met the London-criteria…I was sent to London to meet Dr Paulo Muraro (Consultant Neurologist at Imperial College NHS Trust), who confirmed that I did meet the criteria for treatment… Unfortunately a month later I was advised that NHS Scotland would not support providing treatment in Scotland or finance my receiving treatment in England!.. I had no option but to book whichever clinic abroad would provide me treatment at the earliest opportunity"

We know of patients from Scotland who have received HSCT in England via the NHS for other auto-immune conditions.

Case Study 5 - Patient, Highland

Female, Diagnosed Stiff Person Syndrome age 32, HSCT treatment age 39 - HSCT treatment in Sheffield in December 2018 fully funded by NHS Highland.

Because HSCT is not available on NHS Scotland, patients are forced to travel abroad to access treatment. Patients don't want to have to do this. Arranging treatment abroad is very costly and stressful. Patients often do not have family support during treatment

and experience inconsistent and inadequate post-HSCT care upon their return to the UK.

- **Early HSCT treatment has better outcomes**

Patients want to stop progression or slow accumulation of disability. HSCT received earlier in the treatment of MS has better outcomes as permanent damage is prevented (3). This allows patients to maintain their independence, or return to work and maintain their mobility. In addition, carer's and family members want their loved one to have improved quality of life and their health not to decline further.

Who benefits from HSCT?

Research has demonstrated HSCT halts the progression of MS and has better treatment outcomes than DMT's (4 & 5). In some cases HSCT has helped to reverse disability.

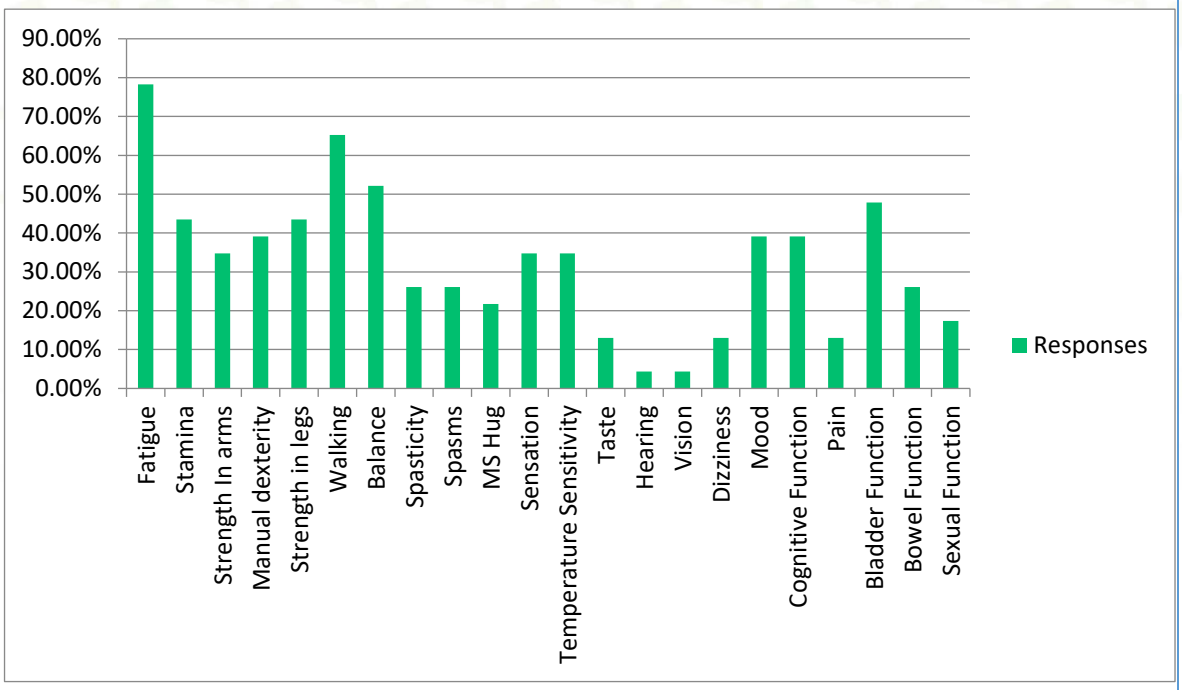
Unlike most other DMTs, HSCT has been shown to benefit patients with all types of MS (RRMS, SPMS and PPMS) for those with active disease as shown by enhanced lesions on an MRI scan. Groups of patients who particularly benefit are RRMS patients with active lesions who are not responding to DMT treatment or where DMTs treatment is contra-indicated.

Patients who benefit less from HSCT, are patients with MS who are responding to DMT treatment. HSCT is also contra-indicated for some patients with progressive forms of MS and a higher level of disability.

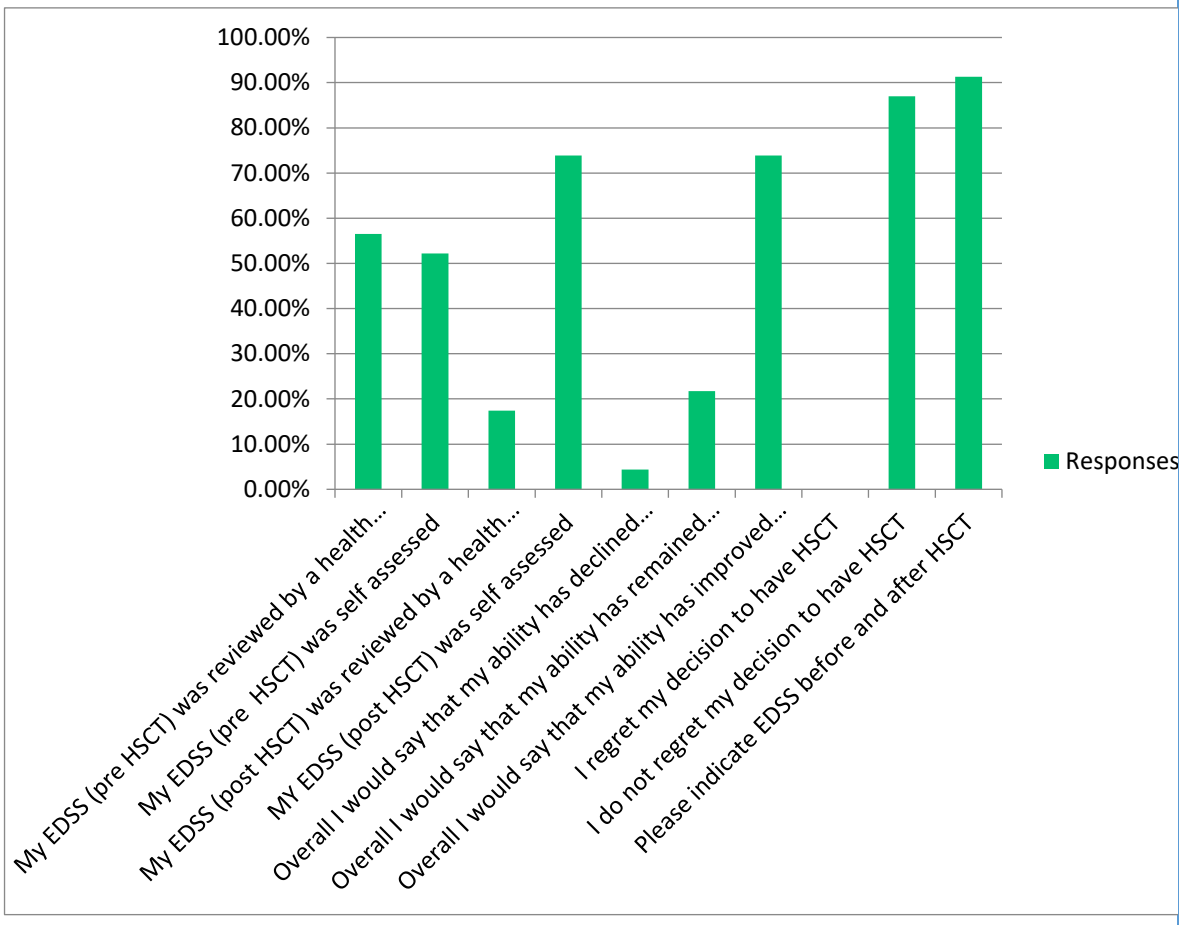
4. What difference did the health technology make to the lives of patients that have used it? (Leave blank if you didn't make contact with anyone who had experience of the health technology.) (See page 9 of guidance.)

Our database shows at least 32 people in Scotland have travelled abroad for HSCT. Of those, 19 have completed both (pre and post) HSCT survey questionnaires. The following summary graphs and statements demonstrate how HSCT has impacted patients:

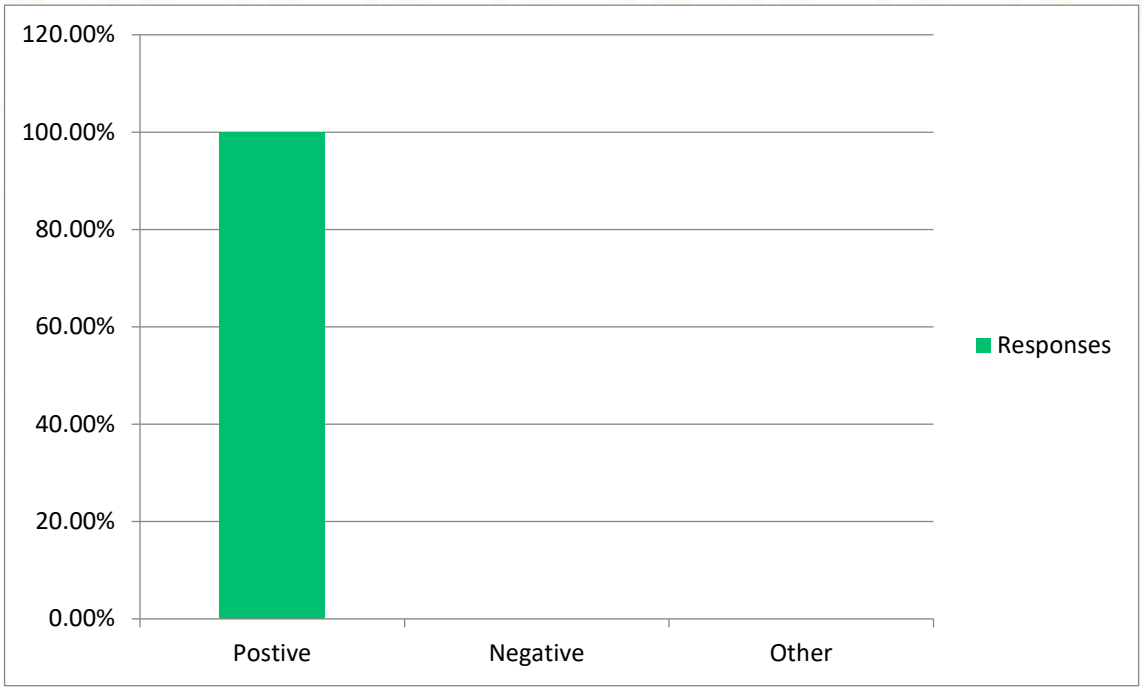
Graph 1 – Symptomatic improvements post HSCT



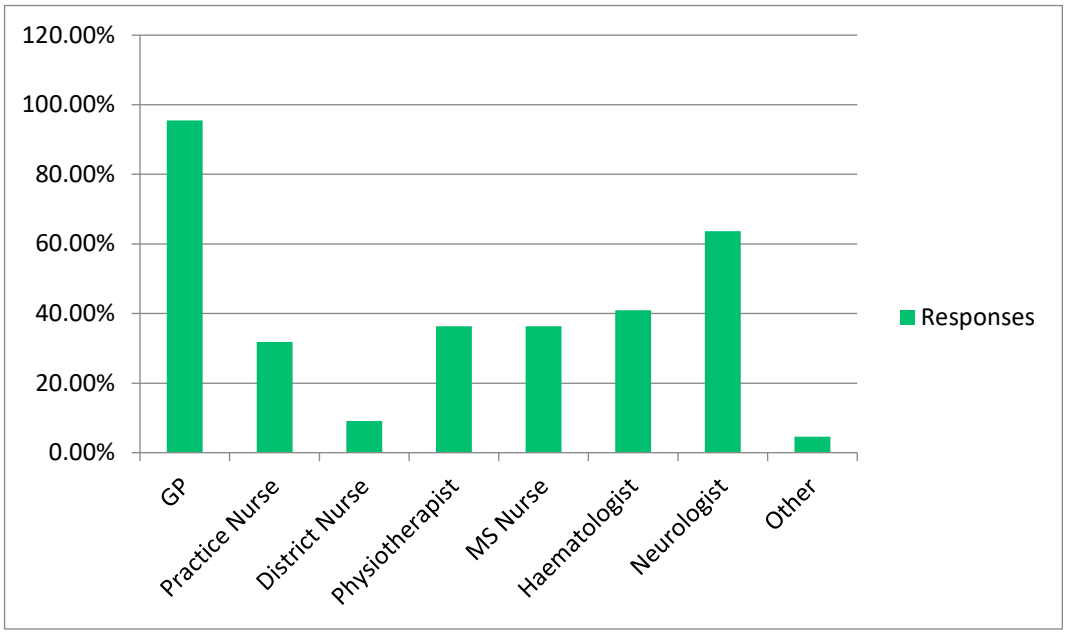
Graph 2 – Information on EDSS post HSCT



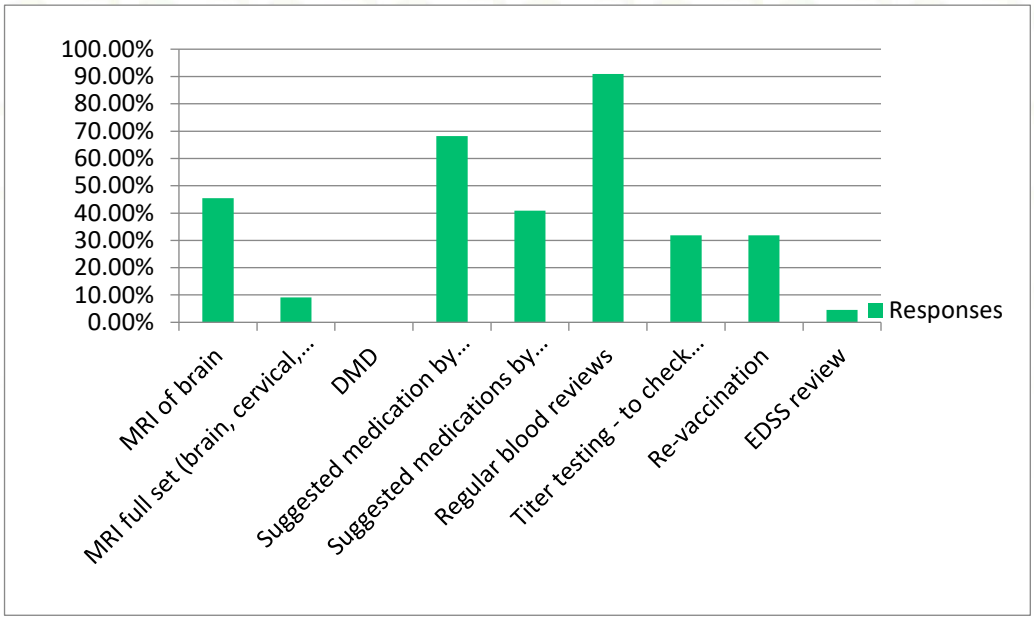
Graph3 – Overall, how would you describe your HSCT experience?



Graph 4 – Support received under NHS Scotland on return to the UK



Graph 5 – Medical reviews / testing / treatments under NHS on return to Scotland?



HSCT Patient 1 Feedback, Lanarkshire

"My main reason for having HSCT was to be here for my children. I was a single parent with no family support when diagnosed and with one relapse after diagnosis, my EDSS went to 6.5. and I ended up having to use a wheelchair. This was life-changing for not only me but my two young children and has impacted our lives hugely. My flares have been severe leaving me paralysed from the neck down at one point and in hospital for 4 months at another point. Trying to consider self-care and child-care in these situations (privately funded) is a huge worry. There's a constant concern that it could happen anytime again and often it can be overwhelming juggling everything but still trying to be Mum, when very ill. Being on DMT's also comes with considerable risks so HSCT gave me hope and I think if you ask most people in a similar situation...the biggest thing that they say that HSCT offers to them is hope."

Carer A, Grampian

"With a SP diagnosis and a lack of any treatment in Scotland we felt the only option to try to stop the progression and try to retain some quality of life was to search for HSCT abroad. It is quite terrifying to go against your Neurologist and take your health into your hands and equally scary flying to Russia and leaving your husband in a hospital in a foreign country. However perhaps equally frightening to watch a gradual decline in mobility with nothing being offered to attempt to halt it ... I just hope that HSCT will become a valid option in Scotland, as it is in England. Scottish patients and their families deserve access to this treatment NOW."

The MS Society has collated figures of the patients that have undertaken the procedure in England, please see Annex 2.

HSCT has risks and limitations and it is important patients are fully aware of these risks before undergoing treatment (6).

HSCT is an invasive, high-risk procedure; all HSCT patients surveyed were aware of the potential risks before their treatment. In addition, a wash out period is required between stopping certain DMT's and having HSCT.

The treatment takes time and there is the potential for side-effects and serious complications. Patients have a lowered immune system after treatment and precautions have to be taken to minimize the risk of infection. Recovery time is required with regular monitoring of bloods by a G.P. A percentage of patients will not respond to HSCT and disease activity and progression will continue.

5. Additional information you believe would be helpful for SHTG to consider. (See page 9 of guidance.)

Below are areas our memberships have particular views and concerns about -

1. The cost of HSCT treatment compared to the cost of DMT treatment

HSCT treatment including after care is a one-off cost compared to the continued cost of DMT treatment. For further information on the accuracy of the following statements see Annex 1.

Case Study 1 - Patient, Forth Valley
"It would appear that the financial implication of me having Tysabri at a cost of approximately £20,000 per year… a total of £160,000 so far is much more expensive that the cost of HSCT!"

Case Study 4 - Patient, Greater Glasgow
I already knew of the Sheffield and London trials before speaking to NHS (GG & C)and via internet groups. I knew that NHS Scotland would not provide it... as mentioned previously NHS in Scotland refused to fund the £30k cost of treatment in London from their budget. All knowledge of treatment options etc. came from my own research, as nothing was offered by NHS.

2. Inconsistent advice and information on HSCT

Inconsistent information and advice are given to patients across different health boards in Scotland. There is evidence that patients are also being given conflicting and inappropriate advice. -

Case Study 2- Patient, Grampian
"Dr. A told me I was crazy and did not recommend I consider such a thing."

"Dr. B was in fact very knowledgeable regarding HSCT, told me he had a few patients who had undergone treatment in Mexico at that time (Nov 2016). Whilst he did not sanction treatment, his recommendation was to make sure If I were going to undergo treatment I should go to an experienced clinic. He also advised me that I could ask my GP to refer me to Dr. Kazmi in London".

"My new Neurologist, Dr. C had a much more open approach. When I advised her I was going for treatment in Russia her response was, 'what support do you need from me?'"

HSCT Patient 2, Grampian

Q. Did you ever discuss HSCT with your Neurologist? - *"I did. I got the usual response that I would come back in a box."*

These areas need to be addressed. Patients need to know they being given the best treatment option for their particular type and stage of MS. Patients need to be made aware of the benefits of HSCT but also the evidenced based side-effects and risks rather than opinion.

6. Please summarise the key points of your submission in up to 5 statements. (See page 9 of guidance.)

- Scotland has the highest prevalence per capita of MS in the UK. MS has devastating consequences for patients, family and carers. MS greatly impacts on the workforce and economy.
- Current treatment options for MS are not effective for all patients and DMT's have serious side effects and risks. HSCT has been proven to halt disease progression and optimal treatment results are obtained when given before disability accumulates.
- Autologous HSCT is already provided on NHS Scotland for cancer patients. Patients with other auto-immune conditions can already be referred and funded for HSCT via reimbursement from NHS England.
- HSCT is a highly effective treatment for some MS patients i.e. RRMS patients not responding to 3rd line DMT treatment. However, HSCT is an invasive treatment with risks and patients need to be informed of the risks and possible complications during treatment and recovery.

- MS patients in Scotland want access to HSCT in Scotland under NHS Scotland. They want the support of NHS Scotland clinicians, family and friends. There is a recognised need for NHS staff to provide accurate and consistent information on HSCT and aftercare.

7. Please give us details of anyone outside your organisation that had a role in preparing your submission. (See page 10 of guidance.)

- Statement of Support from A.I.M.S.

Information about A.I.M.S (Auto Immune and Multiple Sclerosis). Registered Charity No: 1177907

AIMS is the first charity set up in the UK with a focus on helping people who suffer from auto-immune diseases, with a specific focus on multiple sclerosis and HSCT. The Charity has been founded with the aim of signposting, advising and supporting people who wish to find out more about and pursue HSCT as a treatment.

AIMS and The Scottish HSCT Network

AIMS supports the mission of The Scottish HSCT Network. As members of the United Kingdom, there should be parity between MS patients in England, Scotland, Wales and NI. To date, not a single Scottish MS patient has been accepted to have HSCT on the NHS and this is something that has to change. AIMS has had contact with many Scottish patients who wish to undergo HSCT – many of these patients would be accepted for HSCT under the criteria of the London AHSCT MDT. However, because they live in Scotland, they do not qualify and are routinely dismissed by their health practitioners when they raise the issue. In most cases these patients end up going to Mexico or Russia for treatment. While AIMS supports AA Maximov and Clinica Ruiz as centres of excellence for HSCT, Scottish patients should be evaluated for HSCT on the NHS in the same way that their English counterparts are.

- NHS Scotland Pharmacist assistance with sourcing costs of DMT's (publically available on SMC website).
- Oncology Nurse assistance with sourcing HSCT information for cancer patients on NHS Scotland (verbally confirmed information cancer patients are told about HSCT).

References

1. Thompson, A et al (2017) New insights into the burden and costs of multiple sclerosis in Europe: Results for the United Kingdom. The European Multiple Sclerosis Platform *Multiple Sclerosis Journal* Vol. 23(2S) 204–216

2. Muraro,PA et al (2017) Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis. JAMA Neurol. 2017;74(4):459-469. doi:10.1001/jamaneurol.2016.5867

3. Maziarz, R (2019) Autologous Haematopoietic Stem Cell Transplantation in Multiple Sclerosis: a Review of Current Literature and Future Directions for Transplant Haematologists and Oncologists. Open Access Stem Cell Transplantation, Current Hematologic Malignancy Reports pp 1–9

4. Burt, RK et al (2019) Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis: A Randomized Clinical Trial. JAMA. 2019;321(2):165-174. doi:10.1001/jama.2018.18743

5. Muraro, PA et al (June 2017) Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis, Nature Reviews Neurology 13(7)

6. Hatzimichael, E & Tuthill, M (2010) Hematopoietic stem cell transplantation. Stem Cells Cloning. 2010; 3: 105–117. Published online 2010 Aug 26. doi: 10.2147/SCCAA.S6815

8. Do you consent for your submission to be posted on the SHTG website? (See page 10 of guidance.)

Yes [X] No [ ]

Annex 1 – Further information on Costs of HSCT and Disease Modifying Drugs

- Costs of HSCT and DMD Treatment

	Average cost Financial Year 2016-17	Average cost Financial Year 2017-18	Average cost Financial Year 2018-19
Autologous blood stem cell transplant	£16,511.58	£18,030	Available in May 2020
Allogeneic blood stem cell transplant	£60,998.55	£30,157	Available in May 2020

Source-
Freedom of Information request to NHS Scotland.

- Indicative Costs of Certain DMD's

DMD	Cost	Dose Regime
alemtuzumab (Lemtrada)	Cost of 2 year treatment - £56,360 (NICE)	full course of treatment consisting of 5 daily consecutive 12 mg doses in year 1, followed by 3 daily consecutive 12 mg doses 12 months later in year 2
natalizumab (Tysabri)	Annual Cost - £14,730 (NICE) Annual cost - £14,690 (SMC)	300mg IV infusion every 4 weeks
ocrelizumab (Ocrevus)	Annual cost - £19,160 (SMC)	Initial dose: 600mg administered as two separate 300mg IV infusions two weeks apart Subsequent doses: 600mg IV infusion every 6 months

Source -
Lemtrada Costs https://www.nice.org.uk/guidance/ta312/documents/multiple-sclerosis-relapsingremitting-alemtuzumab-fad-document2 on 21/5/19
Tysabri Cost https://www.nice.org.uk/guidance/ta127/documents/multiple-sclerosis-natalizumab-for-the-treatment-of-adults-with-highly-active-relapsingremitting-multiple-sclerosis-final-appraisal-determination5 on 21/5/19
Page 13 of this report contains annual prescription costs for the majority of DMTs
https://www.scottishmedicines.org.uk/media/3966/ocrelizumab-ocrevus-rrms-resub-final-nov-2018-amended-051218-for-website.pdf on 21/5/19

https://www.ema.europa.eu/en/documents/referral/lemtrada-article-20-referral-assessment-report-provisional-measures_en.pdf on 28/5/19

Annex 2 - MS Society Summary on HSCT for MS on NHS England

Who has been treated?

- Of a total of 214 patients who underwent AHSCT for treatment of MS and were registered in a database, 27 were treated in the 7 years between 2002-2014 and 187 were treated between 2015-2019 (5.3 years, incomplete data for 2019)
- The majority of these were paid for by the NHS. 4 of the 2014 of these were paid for privately
- The main driver for the post 2015 increase is the activity is largely due to the formation on the Pan-London MDT
- 151 of the patients who underwent HSCT (70.5% of UK total) did so in London, according to the British Society of Blood and Marrow Transplants (BSBMT) database.

Indicative costs including aftercare

- Circa £28,000 (London figure), but have received estimates as high as £80,000
- Estimated cost to the NHS of procedures (using London figure) £5,964,000

Understanding clinical efficacy

Most up to date study* of 54 patients undertaking treatment in London found that:

- 88% of patients were free from disability worsening 36 months post-transplant
- 12 patients (22.2%) required re-admission following the procedure with a median length of stay of 9 days

- 5 patients (9.3%) developed MRI lesions post AHSCT with a median time to development of 21 months
- Of the RMS patients, 5 (16.7%) experienced symptoms consistent with a clinical relapse post AHSCT at a median time of 11 months
- One RMS patient experienced symptoms consistent with a clinical relapse post treatments, however only one of these patients demonstrated concomitant new lesions on MRI
- Median age of people undertaking the procedure was 41.4yrs
- Median baseline EDSS was 6 (2.0-8.0); median time from diagnosis to AHSCT was 8 years
- 75% of the RMS group had failed a HEDMT. Median number of previous DMTs was 2
- Median inpatient stay for transplant was 22 days
- There was no treatment-related mortality in this cohort

Types of MS of people in the study:

- 55.6%: relapsing MS
- 33.3% secondary progressive MS
- 1.1% primary progressive MS.

* Study published in Multiple Sclerosis Journal *'Autologous stem cell transplantation in multiple sclerosis: the London experience'*

Gaps in research

- There is consensus that a significant gap in understanding is the degree to which HSCT offers advantage over high-efficacy biological therapies such as alemtuzumab and ocrelizumab (rather than the standard efficacy drugs tested in the MIST trial). There is a trial soon to be underway to assess this (STAR-MS). This will be accepting participants early in 2020.
- There is a gap in the understanding of what the return in investment is for the NHS in undertaking HSCT treatment with people in MS. NICE deciding not to undertake a full technology appraisal of HSCT further underlines the importance of this.

Mortality risk

In the first detailed study* published in the Lancet in 2016, 1 patient in a group of 28 died of transplant-related complications.

- The overall risks of transplant related mortality are estimated to be 2% based on EBMT registry data (Muraro et al. Nat Rev Neurol. 2017 Jul;13(7):391-405 – see Figure 5 for review of mortality)
- more recent investigators have claimed that transplant-related mortality is perhaps 0.2%, but there may be problems with data capture and the potential long-term complications of chemotherapy so this is likely to be higher so it is reasonable to assume that HSCT carries a 1-2% mortality rate.

Appendix 2 Patient organisation submission

Patient organisation submission from the Multiple Sclerosis Trust

Healthcare Improvement Scotland | SHTG Advice on health technologies

Patient Organisation Submission Form

Subject of SHTG Assessment

Haematopoeitic stem cell transplantation

Name of patient organisation

Multiple Sclerosis Trust

Health/medical conditions represented

Multiple sclerosis

Contact name for this submission

Janice Sykes

Role of contact person

Information Officer

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Website

www.mstrust.org.uk

Date of submission

21 June 2019

1. Tell us about the sources you used to gather information for this submission. (See page 6 of guidance.)

We have prepared this submission based on our experience of supporting people affected by MS at all stages of the condition. We speak daily to people who are dealing with issues relating to MS: coping with the impact of diagnosis, coping with physical, emotional and financial consequences of MS and making difficult decisions about treatment choices. Stem cell therapies are a regular topic for our enquiry service; over the last three years, we have responded to just over 2 enquiries about stem cells each week (3-4% or our total enquiries), increasing to around 25% when there is media interest.

To support this ongoing interest, we have researched, developed and published evidence-based information on stem cell therapy on our website www.mstrust.org.uk/a-z/stem-cell-therapy and provide updates on the latest developments through our news (example news item) and research pages (example research item).

To gain further insight into the experiences of people receiving HSCT, we sought views on HSCT through social media and interviewed two people who have received stem cell transplants for very active MS at specialist centres in Sheffield and London. We limited our interviews to people treated in England, although additional people came forward who had received treatment overseas. This reflects the limited access to HSCT in England and the demand for this treatment, which is leading to people seeking treatment abroad.

2. What is the health condition and how does it affect the day-to-day lives of patients and their carers? (See page 7 of guidance.)

MS is commonly diagnosed between the ages of 20 and 40, at a time when people are developing careers, starting families, taking on financial obligations. It is a complex and unpredictable condition which has an impact on all aspects of life - physical, emotional, social and economic.

MS is sometimes mild, frequently relapsing remitting, but often progressive with gradually increasing disability. Although the degree of disability will vary, the uncertainty is universal. Even in the early stages of MS, cognition, quality of life, day-to-day activities and the ability to work can be markedly affected. As the disease progresses, increasing disability – such as difficulties in walking – imposes a heavy burden on people with MS and on their families, who often act as informal carers. It also leads to substantial economic losses for society, owing to diminished working capacity.

Good management of MS can be a huge challenge because the disease course is unpredictable, symptoms endlessly variable and the psychosocial consequences can impact as severely as the physical symptoms. People with MS require health services that are responsive to this breadth of need and which take a holistic view of the condition including its impact on the individual and their carers.

Approximately 80% of people with MS have relapsing remitting MS (RRMS). 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 or sexual problems. The invisible consequences of a relapse can 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. Some of these invisible symptoms, such as sexual problems or continence issues are very personal topics and can be difficult to talk about, putting an extra burden on a person with MS to deal with on their own.

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 considerable direct and indirect financial burden, for the individual, their family and the state. They can 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.

Highly active RRMS is a particularly aggressive form of MS, where someone has frequent relapses from the outset or continues to have relapses despite taking one or more of the most effective disease modifying drugs (DMDs). Left unchecked, this can lead to significant disability and loss of independence within a few years of diagnosis.

Research evidence supports early treatment of RRMS with DMDs. This can mean starting with a lower efficacy DMD and switching if there is continued disease activity or starting with one of the more effective DMDs to prevent the build-up of disability.

3. What do patients and carers want from the health technology? (See page 8 of guidance.)

Not surprisingly, people with MS and their carers report that continuing to have relapses and acquire disability despite switching to increasingly more effective DMDs has a huge impact on psychological and physical health and quality of life. Each successive relapse and accumulation of irreversible disability is a reminder that time is running out and people become increasingly desperate to halt the progress of their MS.

Ideally, people want a treatment which at least slows down, preferably stops MS from developing further or, better still, reverses the disease course and restores lost function. Current DMDs for RRMS slow down the course of MS by reducing relapses and accumulation of disability.

While there is a wide range of DMDs available to treat people with RRMS, there is a wide range in people's attitudes to the different drugs. Many factors contribute to a person's preferences for treatments. The balance between benefit and risk is a key factor but other issues are also important such as how well-established a treatment is,

route and frequency of administration, need for routine monitoring all of which can impact daily life, family and work commitments or plans to start a family.

The most effective DMDs which would be recommended for someone with highly active RRMS are associated with serious side effects, for example progressive multifocal leukoencephalopathy caused by natalizumab (Tysabri), secondary autoimmune side effects caused by alemtuzumab (Lemtrada). But there are also significant risks with HSCT, such as hair loss, increased risk of infection, reduced fertility and secondary autoimmunity. With different perceptions of risks and therefore attitudes towards the related risks of either HSCT or the more effective DMDs, treatment decisions are a very personal choice.

People with MS recognize that HSCT is a highly effective treatment for RRMS, with the ability to very significantly reduce the rate of relapses, slow down progression and, in some cases, reverse disability. The aggressive and demanding treatment which carries a degree of risk and involves a lengthy recovery period and time off work makes it unacceptable for some people. But others welcome the potential of HSCT to "hit their MS hard" with a single course of treatment which also reduces the burden of treatment and monitoring for themselves and their families, compared to taking one of the more effective DMDs.

4. What difference did the health technology make to the lives of patients that have used it? (Leave blank if you didn't make contact with anyone who had experience of the health technology.) (See page 9 of guidance.)

We were able to hold one-to-one discussions with two people who have had HSCT at specialist centres in England.

The first person, diagnosed with RRMS in 2007, had never been prescribed one of the DMDs. After researching HSCT extensively, she felt it offered the best chance of halting her MS and to continue looking after her young family and remain in work. As she did not meet the criteria for NHS treatment she had HSCT at a private London hospital in early 2019. She acknowledged that the treatment had been tough, but no more than she had anticipated and the hospital staff had been quick to resolve any problems she was experiencing. She received her stem cell infusion about two months ago and is now back at home recovering slowly. She expects to be able to resume work and family commitments later this year, roughly five months after receiving her stem cell infusion. At the time of our conversation, it was too early for her to know the effect of HSCT on her MS activity but she was extremely glad she had been able to have HSCT.

The second person was diagnosed with RRMS in 2013, initially prescribed interferon beta 1a (Rebif), switched to fingolimod (Gilenya) but continued to have relapses. In the 12 months prior to HSCT, he had 8 relapses (average for most people is one relapse every two years) and an MRI scan revealed many active lesions. He was referred to Sheffield, accepted for HSCT and received his stem cell infusion in January 2018. Overall, he coped well with the treatment; main problems were hair loss and contracting an infection while in the hospital which was treated with antibiotics. A recent MRI scan has shown no new MS activity and he has felt very well, although an infection during the winter knocked him back but he is now improving again. For him, the greatest benefit has been stopping relapses, which over the previous 5 years had left him dependent on a wheelchair for extended periods and resulted in early medical retirement. With his health now stabilized, he is able to concentrate on building up his strength and is very optimistic about the future. He believed that if he had been able to access HSCT in the first two years after diagnosis, before MS had caused more damage, he would still be working.

Both of the people we spoke to emphasized the importance of remaining as mobile as possible during their hospital stay and following a program of exercises to rebuild strength during the recovery period. They both felt this was vital to ensure they got the maximum benefit from HSCT. Their experiences highlighted the importance of joined-up services such as cooperative working between haematology and neurology and incorporating referral to a community physiotherapy team into the HSCT treatment plan to avoid delay in accessing services after returning home.

5. Additional information you believe would be helpful for SHTG to consider. (See page 9 of guidance.)

There is huge interest in HSCT from people with MS, with increasing numbers seeking treatment overseas. At the moment, there is nowhere in Scotland offering this treatment and it is very difficult, if not impossible, for people in Scotland to get NHS funding for treatment in England. We welcome this assessment which we hope will lead to more equitable access to HSCT for those meeting the criteria.

HSCT, just like the DMDs, is more effective when used early before MS causes too much damage. It is a demanding treatment, so people are likely to do better if they have this treatment before they are more severely affected, and it should not be considered a treatment of last resort. The more effective DMDs may be contra-indicated for an individual; without access to HSCT they would be left with inadequately treated highly active RRMS.

As well as treating people who have continued to have relapses despite taking one of the more effective DMDs, HSCT would also be appropriate as a first line treatment for someone with very active and aggressive relapsing remitting MS from the outset (known as rapidly evolving severe RRMS, a subgroup currently recognised for DMDs such as fingolimod and cladribine). We would recommend that SHTG and NHS Scotland recognise this additional group of patients when drawing up criteria for treatment.

HSCT is an established treatment and has been incorporated into the NHS England Treatment Algorithm for Multiple Sclerosis Disease-modifying Therapies as a third line treatment.

6. Please summarise the key points of your submission in up to 5 statements. (See page 9 of guidance.)

- MS is a complex and unpredictable condition which has an impact on all aspects of life; early proactive treatment is essential to prevent future disability.
- Continuing to have relapses and acquire disability despite switching to increasingly more effective DMDs takes a heavy toll on psychological and physical health, and quality of life, employment and financial status, not only for the person with MS but also for their family who often act as informal carers.
- HSCT is a highly effective treatment for RRMS, with the ability to very significantly reduce the rate of relapses, slow down progression and, in some cases, reverse disability, giving people hope for a better quality of life in the long term.
- As a one-off therapy, HSCT reduces the burden of treatment and monitoring for both people with MS, their families and the NHS compared with DMDs. However, the demands of the treatment may not suit everyone; as with the DMDs, an individual and their MS team will need to consider the risks and benefits of HSCT before deciding whether it is the right treatment for them.
- Extensive clinical evidence supports the use of HSCT; internationally, it is an established treatment for people with highly active relapsing remitting MS and it is important that people living in Scotland are not denied access to this innovative treatment.

7. Please give us details of anyone outside your organisation that had a role in preparing your submission. (See page 10 of guidance.)

8. Do you consent for your submission to be posted on the SHTG website? (See page 10 of guidance.)

Yes ✓ No