Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Autologous haematopoietic stem cell transplantation to treat people with previously treated relapsing-remitting multiple sclerosis

1. Purpose of the evidence appraisal report

This evidence appraisal report (EAR) aims to identify and summarise evidence that addresses the following question: is autologous haematopoietic stem cell transplantation clinically and cost-effective for previously treated, relapsing-remitting multiple sclerosis?

EARs are based on rapid systematic literature searches, with the aim of identifying the best published clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. This EAR is adapted from the advice statement produced by the Scottish Health Technologies Group (SHTG), "Autologous haematopoietic stem cell transplant for patients with highly active relapsing remitting multiple sclerosis not responding to high-efficacy disease modifying therapies", published in 2019. The draft EAR is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Health problem

Multiple sclerosis (MS) is a chronic immune-mediated condition of the central nervous system, most commonly affecting young, active people in employment (Sharrack et al. 2019, Multiple Sclerosis Trust 2019a). The aetiology of MS is multifactorial and involves the interaction of genetic and environmental factors in a complex manner (Tintore et al. 2019). MS can be severely disabling and typically has two clinical phases, a relapsing phase and a progressive phase. The term 'relapsing MS' covers both relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) with superimposed relapses. RRMS is characterised by repeated episodes of neuro-inflammation, which can cause demyelination and axonal damage, but these episodes eventually resolve (Das et al. 2019). Approximately 80-85% of people with MS have RRMS at onset (NICE 2019). A minority of people with RRMS may be diagnosed with one of two different RRMS subtypes, highly active RRMS (HA-RRMS) or rapidly evolving severe RRMS (RES-RRMS) (NHS England 2019). MS symptoms are wide-ranging and include cognitive, visual and sensory disturbances, limb weakness, gait problems, bladder and bowel dysfunction. Although there may be respite from symptoms during periods of remission, over time around two thirds of patients develop progressive disability and the diagnosis is changed to SPMS (NIHR Innovation Observatory 2016).

Once a patient meets starting criteria for MS, treatment approaches include several different immunomodulatory disease modifying therapies (DMTs), according to a treatment algorithm published by NICE (NHS England 2019). As the majority of DMTs target neuro-inflammation with

the aim of reducing relapse rates (and associated symptoms), they are most likely to be effective for the relapsing-remitting phase of MS (Snowden et al. 2018). Medicines licensed for this phase of MS include beta-interferon products (1a products Avonex® and Rebif® and also 1b products Betaferon® and Extavia®), peginterferon beta (Plegridy®), dimethyl-fumarate (Tecfidera®), glatiramer acetate (Brabio®, Copaxone®), teriflunomide (Aubagio®), fingolimod (Gilenya®), alemtuzumab (Lemtrada®), cladribine (Mavenclad®), ocrelizumab (Ocrevus®) and natalizumab (Tysabri®). The latter four medicines are considered high-efficacy DMTs as they typically enable a much higher reduction in relapse rate, however, they are also associated with a higher risk of adverse events. Specialist clinicians advised HTW researchers that it is rare for patients to exhibit inflammatory breakthrough disease activity while on appropriate, high-efficacy DMTs (Expert Comment, 09 January 2020, 16 March 2020). However, they also acknowledged that these DMTs may no longer be effective in a small proportion of patients (Expert Comment, 30 December 2020; Expert Comment, 09 January 2020; Expert Comment, 20 January 2020). Due to the lack of licensed DMTs ains MS progresses and becomes a neurodegenerative disease, early intervention at the relapsing-remitting phase is key to preventing long-term disability. Two agents are indicated for SPMS; beta-interferon products Betaferon® and Extavia®) and siponimod fumaric acid (Mayzent®), indicated for the treatment of adult patients with SPMS with active disease characterised by relapses or imaging features of inflammatory activity (received licence January 2020). Ocrelizumab (Ocrevus®), a recombinant monoclonal CD20 antibody, is indicated for early primary progressive multiple sclerosis (PPMS) (which has imaging features characteristic of inflammatory activity) (NHS England 2019).

The annual incidence of MS has been estimated to be 7 per 100,000 people in Wales while the annual prevalence has been estimated to be 179 per 100,000 people (MS Society 2020). There is some variability in the literature, possibly due to the distribution of MS being uneven around the UK (and the world), with prevalence generally increasing as you travel away from the equator. These estimates would equate to 230 new MS patients in Wales every year and a prevalence of 5,600 people (MS Society 2020). Of the 5,600 people in Wales with MS, approximately 5,040 people would have RRMS at onset, while 560 people would have a progressive form of MS.

3. Health technology

Autologous haematopoietic stem cell transplantation (AHSCT) is an intensive, inpatient, one-off, therapeutic procedure which aims to reset a patient's immune system and so halt disease progression. AHSCT consists of a number of steps which take place over a timeframe of six months or more, depending on patient recovery (NIHR Innovation Observatory 2016, Das et al. 2019, Multiple Sclerosis Trust 2019b).

1. Pre-transplant wash out: DMTs are discontinued as early as possible to minimise both risks to the patient and inhibitory effects on successful stem cell mobilisation.
2. Haematopoietic stem cell (HSC) mobilisation: the patient is given medicines, typically cyclophosphamide (Cyc) and granulocyte-colony stimulating factor (G-CSF), which encourage the movement of HSCs from the bone marrow into the peripheral blood.
3. HSC harvesting and storage: once mobilisation is at an optimal level, HSCs are collected from the peripheral blood by apheresis machine, typically 10 days later. The apheresis machine separates HSCs from the patient's blood, which is returned to them, and the HSCs are frozen until they can be returned to the patient.
4. Conditioning chemotherapy: depending on the conditioning regimen used (Table 1), the patient's self-reactive immune cells are either partially eliminated or completely eradicated from the bone marrow and immune system. This may take several days. Intermediate intensity, myeloablative regimens and intermediate, non-myeloablative regimens are most frequently used in recently published literature (Table 1).

5. Transplantation: the patient's frozen HSCs are thawed and returned to them by infusion; this may take several hours. Over the next 10 to 30 days, in a process called engraftment, the HSCs migrate to the patient's bone marrow where they then start producing new blood and immune cells. Until the patient is once again able to produce a sufficient number of cells to maintain a healthy blood count and innate immunity, a high level of supportive care including antibiotics, transfusions, symptomatic care, growth factors and monitoring, is required to bring them through the engraftment period.
6. Post-transplant care: due to the intensive nature of AHSCT patients require several months to recover. During this time patients also undergo monitoring. Initially this is focused on prevention and treatment of infections as well as early post-transplant complications. Over time regular monitoring focuses on the disease course as well as late post-transplant complications.

Due to the many complex steps involved, 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) recommends that only units with expertise both in the management of MS and AHSCT should offer AHSCT. A service specification document, supporting the Welsh Health Specialised Services Committee (WHSSC) policy position "Haematopoietic stem cell transplantation for adults", lists six providers of AHSCT for Welsh adults, four of which are located in England (WHSSC 2020b, WHSSC 2020a). Conditioning regimens in Wales follow international protocols (Expert Comment, WI). Welsh multi-disciplinary teams (MDTs) would likely follow EBMT recommendations for conditioning regimens for MS, while also taking advice from current UK centres delivering AHSCT for MS in order to harmonise the approach (Expert Comments, GI, WI).

Clinical experts representing Cwm Taf Morgannwg and Cardiff and Vale University Health Boards estimate that within their catchment, there are around 1-5 people with inadequately controlled disease despite high efficacy DMTs who would be eligible for treatment with AHSCT (Expert Comments, 30 December 2019, 02 January 2020). A clinical expert representing Swansea Bay and Hywel Dda University Health Boards estimates that 1-5 patients within their catchment area would be eligible for treatment with AHSCT every year (Expert Comment, 17 February 2020). A clinical expert representing Betsi Cadwaladr Health Board states that no patients are believed to currently fulfil NHS criteria for AHSCT, but that the treatment may be considered for a very small number of patients in the future (Expert Comment, 10 January 2020). Following completion and in the event of favourable results from ongoing clinical trials, demand for AHSCT will likely increase and, according to clinical experts with direct experience of carrying out this procedure for MS patients, the above eligibility estimates are considered to be an underestimate (Expert Comments, 17 February 2020, 25 February 2020, 16 March 2020).

Table 1. Conditioning regimens used for AHSCT, adapted from Sharrack et al. (2019)

Intensity	Examples of conditioning regimen
High	Total body irradiation (TBI), cyclophosphamide and anti-thymocyte globulin (ATG)
	Busulfan, cyclophosphamide and ATG
Intermediate (myeloablative)	Carmustine (brand name BCNU) 300 mg/m^2, etoposide 800 mg/m^2, cytarabine arabinoside 800 mg/m^2 and melphalan 140 mg/m^2 (BEAM, with total doses of chemotherapy provided) and ATG ('BEAM-ATG')
Intermediate (lymphoablative/nonmyeloablative)	Cyclophosphamide 200 mg/kg and rabbit ATG (Cyc-ATG)

Low	Chemotherapy only* regimens e.g. single agent cyclophosphamide 100 mg/kg for mobilisation and repeated 100 mg/kg for conditioning (without rituximab)
Please note doses are examples and the authors do not take responsibility for drug and doses administered, which lies with individual authorised prescribers in haematopoietic stem cell therapy units. Doses and types of ATG vary between published regimens.	
*Addition of serotherapy (*i.e.* antibody therapy) to chemotherapy renders the regimen 'intermediate-intensity'	

4. Current guidance and advice

Advice published in 2019 by the Scottish Health Technologies Group (SHTG) made the following recommendations:

> *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* (SHTG 2019).

The Multiple Sclerosis International Stem Cell Transplant Trial (MIST) randomised control trial (RCT) described in the SHTG advice statement compared AHSCT (n = 55) with DMTs (n = 55) in patients with RRMS which remained highly active despite DMTs (Burt et al. 2019). Alemtuzumab and ocrelizumab were not comparators in this trial, the former due to the potential risk of complications that might prevent cross-over from the DMT group to the AHSCT group and the latter was not yet licensed. The most frequently received DMTs were natalizumab and dimethyl fumarate. Mean follow-up was 2.8 years and the primary outcome was time to disease progression, the assessment of which was blinded. AHSCT was found to significantly prolong time to disease progression compared with DMTs, hazard ratio 0.07 (95% CI: 0.02 to 0.24, $p < 0.001$). The group noted that the profile of DMTs to which the patients had been exposed prior to consideration for AHSCT in this trial was different from current Scottish practice.

The systematic review and meta-analysis described in the SHTG advice statement analysed 15 studies, 10 prospective and five retrospective (n = 764) (Sormani et al. 2017). The findings of seven studies with ≥ 44% RRMS patient populations (n = 414) were compared with eight studies with < 44% RRMS patient populations (n = 350) and presented in a subgroup analysis. Transplant-related mortality (TRM) was 2.1% in the total population (95% CI: 1.3% to 3.4%), 1% in the ≥ 44% RRMS patient population (95% CI: 0.4% to 2.6%) and 3.4% in the < 44% RRMS patient populations (95% CI: 1.9% to 6%). The interaction between the subgroups was statistically significant (p = 0.028). Two-year progression was 17.1% in the total population (95% CI: 9.7% to

24.5%), 7.8% in the ≥ 44% RRMS patient population (95% CI: 1.3% to 14.2%) and 24.8% in the < 44% RRMS patient populations (95% CI: 16.7% to 32.9%). The interaction between the subgroups was statistically significant (p = 0.004). The findings of eight studies with pre-2005 patient populations (n = 415) were compared with seven studies with post-2005 patient populations (n = 349) and presented in a sub-group analysis finding TRM to also be associated with transplant year. TRM was 3.6% for pre-2005 studies (95% CI: 2.2% to 6%) and 0.3% for post-2005 studies (95% CI: 0% to 2%), with the interaction between subgroups being statistically significant (p = 0.014). The findings of eleven studies with patient populations of expanded disability status scale (EDSS) > 5.5 (n = 292) were compared with four studies with patient populations of EDSS ≤ 5.5 (n = 472) and presented in a subgroup analysis finding TRM to also be associated with baseline EDSS. TRM was at 3.2% for EDSS>5.5 (95% CI: 1.8% to 4.6%) and 0.3% for EDSS ≤ 5.5 (95% CI: 0% to 2.1%). The interaction between the subgroups was also statistically significant (p = 0.001).

Guidelines from the EBMT Autoimmune Diseases Working Party and JACIE were published in 2019 (Sharrack et al. 2019). The guidelines recommend the following:

> *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. Evidence best supports treatment in patients who are able to ambulate independently (EDSS 5.5 or less), who are younger than 45 years and have disease duration less than 10 years.*
>
> *Patients with 'aggressive' MS, who develop severe disability in the previous 12 months, are suitable candidates for AHSCT. Given the potential for irreversible disability, such patients may be considered even before failing a full course of DMT.*
>
> *Patients with SPMS should be considered for AHSCT, preferably in a prospective clinical trial, only when inflammatory activity is still evident (clinical relapses and Gd-enhancing or new T2 MRI lesions) with documented disability progression in the previous 12 months.*
>
> *Patients with PPMS should be considered for AHSCT, preferably in a prospective clinical trial, only when inflammatory activity is evident (Gd-enhancing and new T2 MRI lesions) with documented evident disability progression in the previous 12 months.*
>
> *Paediatric patients with MS who have breakthrough inflammatory disease with less toxic treatments may be considered for AHSCT.*
>
> *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* (Sharrack et al. 2019).

An MS treatment algorithm illustrating the position of AHSCT in England was developed by NHS England's Neuroscience Clinical Reference Group in September 2018, updated in March 2019, and 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 (NHS England 2019).

The Association of British Neurologists (ABN) developed the following statement on autologous haematopoietic stem cell treatment of multiple sclerosis published in 2016:

> *The Association of British Neurologists welcomes recent research into autologous haematopoietic stem cell treatment of multiple sclerosis. Despite many advances in the treatment of this disease, for some people it is disabling and life-limiting. New therapies which combine high efficacy with acceptable side-effects are certainly needed. However, as a recent commentary put it "the jury is still out regarding the appropriateness and indications of haematopoietic stem cell treatment for multiple sclerosis" (Soldán & Weinshenker, 2015).*
>
> *Autologous haematopoietic stem cell treatment should only be seen as a potential immunotherapy in multiple sclerosis; there is no suggestion that these stem cells are reparative. Therefore, there is no rationale for its use in people with progressive multiple sclerosis* (Association of British Neurologists 2016).

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):

> *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.*
>
> *Patients most likely to benefit from I/AHSCT are relatively young e.g. 50 years of age or less, with relatively short disease duration e.g. 5 years or less, have active relapsing-remitting multiple sclerosis and accumulating disability but still are ambulatory, and have ongoing disease activity despite DMT. I/AHSCT is unlikely to benefit patients with longstanding progressive multiple sclerosis without recent inflammatory features (clinical relapses or MRI lesion activity)* (Scolding et al. 2017).

NICE published a rapid guideline on HSCT and COVID-19 in April 2020, which was updated on 29 July 2020. The guideline aims to maximise the safety of patients undergoing HSCT while making best use of NHS resources and protecting staff from infection (NICE 2020).

5. Evidence search methods

The Population-Intervention-Comparator-Outcomes (PICO) framework for the evidence appraisal (Appendix 2) was developed following input from the Health Technology Wales (HTW) Assessment Group, SHTG and UK experts.

A systematic literature search was undertaken on 19 November 2019. The search was an update of that performed by SHTG and the dates were restricted to between April and November 2019 to reflect this (SHTG 2019). Follow-up searches were undertaken on 16 March 2020 and 22 June 2020. The search strategy used by HTW was provided by SHTG and is available on request. Databases searched included Medline, Embase, CINAHL and the Cochrane database of systematic reviews. Background studies and other papers identified at the scoping stage, as well as the SHTG report, were also assessed and included when relevant.

Identified studies were only included if outcomes were reported for people with MS but included RRMS (or for related terms as per the PICO framework). Patient safety and organisational issues were identified from the papers included in the clinical effectiveness section and expert advice; no specific searches were undertaken.

6. Clinical effectiveness

One RCT (MIST) was included in the SHTG advice statement and no further RCTs comparing AHSCT with current practice for people with MS (specifically RRMS or related terms) were identified in this update (Burt et al. 2019, SHTG 2019). Four systematic reviews were included in this evidence appraisal report which considered AHSCT in MS patients (specifically RRMS patients or related terms).

The first review, Ge et al. (2019), contained 18 studies (n = 732). Ten of these studies used patient populations which completely or overwhelmingly comprised progressive MS patients and therefore do not match the PICO statement for this report. Characteristics of the remaining eight studies, some of which were included in the SHTG advice statement (2019), are detailed in Table 6 (Appendix 3). Ge et al. (2019) aimed to provide an evaluation of the long-term efficacy and safety of AHSCT in MS treatment, and to optimise its benefit/risk ratio. Subgroup analysis on conditioning regimens found that low- and intermediate-intensity regimens were associated with a higher progression-free survival (PFS) of 80% (95% CI: 75% to 85%) compared with 58% (95% CI: 40% to 75%) for high-intensity regimens. RRMS patients were found to benefit more from AHSCT than other MS clinical types as this group had a PFS of 85% (95% CI: 77% to 92%). Patients with gadolinium-enhanced (active) lesions at baseline MRI responded better to AHSCT, PFS 77% (95% CI: 0.61 to 0.94), than those without these lesions at baseline MRI, PFS 47% (95% CI: 0.33 to 0.62). TRM was estimated at 1.34% (95% CI: 0.39% to 2.3%, p = 0.058), but it was higher in studies using high-intensity regimens (3.13%) compared with intermediate-intensity regimens (0.97%), and higher also in studies performed before 2006 (1.93%). The review's measure of overall mortality was 3.58% (95% CI: 2.40 to 4.86, I^2 = 64.7%, p = 0.000). The authors concluded that AHSCT can induce long-term remissions for MS patients with a high degree of safety. Low- and intermediate-intensity regimens and RRMS patients with the presence of gadolinium enhanced lesions at baseline MRI could obtain an optimal benefit/risk ratio from AHSCT.

The second review, Sormani et al. (2017), contained fifteen studies, twelve of which had been in included in Ge et al. (2019). The Sormani et al. (2017) systematic review was included in the SHTG advice statement (SHTG 2019). Sormani et al. (2017) is described in Section 4 of this report.

The third review, Li et al. (2016), contained eight studies. Five considered patient populations with progressive MS while one study did not categorise the patient population into a subtype and are therefore not applicable to this evidence appraisal report (Fagius et al. 2009, Kozak et al. 2000, Carreras et al. 2003, Xiu-shi et al. 2005, Xu et al. 2006, Bowen et al. 2012). One other study, Krishnan et al. (2008), in the RRMS patient population, investigated the use of high-dose chemotherapy and not AHSCT and is therefore not applicable. Study characteristics for the remaining study which was included in the Li et al. (2016) systematic review are detailed in Table 6 (Appendix 3) (Burt et al. 2009).

The fourth systematic review included in this evidence appraisal report was identified during the update search. Zhang & Liu (2020) contained 24 studies. Eighteen studies had been included in Ge et al (2019), two studies had been included in SHTG (2019), and two studies were included in this report prior to the update search. The systematic review included two additional studies, which are described in Table 6 (Appendix 3) (Frau et al. 2018, Tolf et al. 2019). Zhang & Liu (2020) aimed to assess the effect and safety of AHSCT in the treatment of MS and neuromyelitis optica spectrum disorder. In relation to MS, PFS following AHSCT was 74% (95% CI: 69% to 79%). Sub-group analyses on conditioning regimens found that low-, intermediate- and high-conditioning regimens were associated with a PFS of 85% (95% CI: 69% to 101%), 73% (95% CI: 68% to 79%) and 58% (95% CI: 37% to 79%) respectively. Sub-group analyses on MS clinical types found that RRMS, PPMS and SPMS were associated with a PFS of 81% (95% CI: 70% to 93%), 78% (95% CI: 66% to 90%)

and 60% (95% CI: 51% to 68%) respectively. The authors concluded that AHSCT had a long-term effect on MS patients with a high degree of safety and that optimal benefit was found for RRMS patients and for patients receiving low- and intermediate-intensity regimens.

Ten additional primary studies were included in this evidence appraisal report which were not included in the systematic reviews. Characteristics of these studies are described in detail in Table 6 (Appendix 3). One study was identified from SHTG (2019), while five studies were identified in the literature search (Muraro et al. 2017b) (Bose et al. 2019, Comini-Frota et al. 2019, Mehra et al. 2019, Moore et al. 2019, Ruiz-Arguelles et al. 2019). An additional four primary studies were identified in update searches for this evidence appraisal report (Tappenden et al. 2019, Boffa et al. 2020, Kvistad et al. 2019, Dayama et al. 2020).

6.1 Clinical outcomes

Table 7 (Appendix 4) summarises the results reported by the relevant primary studies from each included systematic review and the additional ten primary studies, for each clinical outcome following AHSCT. The proportion of people in each study with RRMS is also given in Table 7 (Appendix 4), as outcomes were not usually reported by MS subtype. Where outcomes were reported separately for people with RRMS, these have also been included.

Following AHSCT, people with MS experienced a decrease in annualised relapse rate compared with the rate prior to AHSCT in four studies (Casanova et al. 2017, Boffa et al. 2020, Burman et al. 2014, Krasulova et al. 2010). For five non-comparative studies, relapse-free survival (RFS) was above 80% for at least two-years post-AHSCT (Moore et al. 2019, Nash et al. 2017, Burt et al. 2015, Burman et al. 2014, Mancardi et al. 2012). One of these studies (Nash et al. 2017) reported RFS specific to the RRMS patient population. A further study in the RRMS population reported an RFS of 76% after a mean of 37 months (range 24 to 48 months) (Burt et al. 2009). One study (non-randomised) also reported RFS above 80% for its AHSCT group while RFS was 69% in the group receiving alemtuzumab (Boffa et al. 2020); the difference was statistically significant ($p = 0.012$). For frequency of relapse in the year post-AHSCT, the MIST RCT, reporting on an RRMS patient population, found a significant difference ($p < 0.001$) between the AHSCT (2%) and DMT (69%) arms (Burt et al. 2019).

The proportion of patients with disease progression was reported by the MIST RCT (Burt et al. 2019). In both AHSCT and DMT arms, the proportion of patients displaying disease progression increased over a five-year timeframe post-AHSCT. However, the proportion of patients with disease progression was much lower for those receiving AHSCT, 1.92% at one year compared with 24.5% for patients remaining on DMTs. At five years this proportion was 9.71% for those receiving AHSCT compared with 75.3% for those remaining on DMTs (statistical analysis was not provided for these comparisons as the MIST RCT permitted crossover between arms after the primary endpoint). One matched adjusted indirect comparison reported a hazard ratio for sustained EDSS progression of 0.11 for AHSCT versus natalizumab (95% confidence intervals 0.01 to 0.76) (Tappenden et al. 2019).

PFS varied amongst reported studies with the proportion of patients having survived progression free five-years post-AHSCT ranging from 46 to 77% (Muraro et al. 2017b, Nash et al. 2017, Burman et al. 2014, Mancardi et al. 2012); one of these studies reported on an RRMS patient population (Nash et al. 2017). Two studies reported outcomes separately for patients with RRMS and at a shorter timeframe than five-years. Moore et al. (2019) reported PFS for RRMS as 95% at one year and 88% at two- and three-years post-AHSCT with these values being statistically significantly better than rates for SPMS patients ($p = 0.04$). Similarly, Krasulova et al. (2010) reported a statistically significant difference ($p<0.001$) in PFS for RRMS patients (84.4% at three years post-AHSCT) compared with SPMS patients (60%).

Disease free progression also varied amongst reported studies with the proportion of patients having progressed five-years post-AHSCT without any disease events ranging from 68% to 69.2% (Nash et al. 2017, Burman et al. 2014); one of these studies reported on an RRMS patient population (Nash et al. 2017). This proportion was similar for studies reporting at shorter time-frames (Atkins et al. 2016, Burt et al. 2015). Two studies reported outcomes separately for patients with RRMS and at a shorter timeframe than five-years. Moore et al. (2019) reported disease free progression for RRMS as 90% at one year and 70% at two- and three-years post-AHSCT compared with a total proportion of patients as 82%, 65% and 60% at one-, two- and three-years post-AHSCT. Shevchenko et al. (2015) reported disease free progression for RRMS as 83.3% at a median follow-up of 48.9 months post-AHSCT compared with 75.5% for progressive types of MS, though the difference between groups was not statistically significant ($p > 0.05$).

No evidence of disease activity (NEDA) has not been frequently used within clinical practice as an outcome measure to date but this is changing as it is considered to be the new gold standard for efficacy (Expert Comment, 17 February 2020). The MIST RCT, reporting on an RRMS patient population, found that the proportions of patients with NEDA (analogous to NEDA-3) were significantly different ($p < 0.001$) between the DMT and AHSCT groups in favour of AHSCT (Burt et al. 2019). Two retrospective studies, reporting on RRMS patient populations, found that NEDA-3 was reached by 76% (n = 13 of 17) at 24 months post-AHSCT and by 70% (n = 10) at five years post-AHSCT (Tolf et al. 2019, Kvistad et al. 2019). One of these two studies reported on NEDA-4 (analogous to sustained complete remission), finding that it was reached by 50% (n = 10) at five years post-AHSCT (Tolf et al. 2019). Moore et al (2019) reported NEDA probability for RRMS to be 94% at one-year post-AHSCT and 75% at two- and three-years post-AHSCT. Boffa et al. (2020) compared NEDA-3 between AHSCT and alemtuzumab treated patients (non-randomised) and found the difference between treatment groups to be statistically significant ($p = 0.023$). Casanova et al. (2017) compared NEDA (percentage of patients with either relapse or progression) between RRMS and SPMS patients, finding the difference between clinical groups to be statistically significant ($p = 0.004$).

Expanded disability status scale (EDSS) was the most frequently reported outcome in the present studies. For the most part, EDSS decreased from baseline to various defined times, specifically one-, two- or three-years post-AHSCT (Burt et al. 2015, Burt et al. 2009, Burman et al. 2014, Nash et al. 2017, Moore et al. 2019, Tolf et al. 2019); three of these studies reported on an RRMS patient population (Nash et al. 2017, Burt et al. 2009, Tolf et al. 2019) (Dayama et al. 2020). Kvistad et al. (2019) also reported on an RRMS population where 50% of its patients experienced stabilisation of EDSS while 43% experienced sustained improvement. Bose et al. (2019) reported an increase in EDSS, from 5 at baseline to 5.5 at trial's end, however, this change was not statistically significant. Four studies reported RRMS specific-EDSS outcomes. Mancardi et al. (2012) compared the decrease in EDSS between RRMS and SPMS patients at one-year post-AHSCT, whether it was > 1, between 0.5 and 1 or no change, and the difference between groups was statistically significant ($p = 0.009$). Casanova et al. (2017) also compared the decrease in EDSS between RRMS and SPMS patients but at a minimum of two-years post-AHSCT. While EDSS decreased, from 5 at baseline to 3.4, for RRMS patients, it increased, from 6.1 to 7.2, for SPMS patients (statistical analysis was not provided for this comparison). Muraro et al. (2017b) similarly compared the decrease in EDSS between RRMS and SPMS patients at one-year post-AHSCT, whereby a decrease of 0.76 was reported for RRMS patients and a decrease of 0.14 was reported for SPMS patients (statistical analysis was not reported for this comparison).

Neurologic rating scale (NRS) is not frequently reported in the literature, however the MIST RCT reported a difference in means from baseline to one-year post-AHSCT for RRMS patients who either received AHSCT or remained on DMTs (Burt et al. 2019). With 0 being the worst score and 100 the best, the value increased for the AHSCT group while it decreased for the DMT group. The

between group difference in means was 11.2 and the comparison was statistically significant ($p = 0.001$).

Four studies reported measures of neurological impairment which include the Multiple Sclerosis Functional Composite (MSFC), nine hole peg test and the Paced Auditory Serial Addition Test (PASAT). The results of these studies are presented in table 8 (Appendix 4). Three studies reported MSFC (Burt et al. 2019, Burt et al. 2015, Nash et al. 2017). The MIST RCT reported a statistically significant improvement ($p < 0.001$) for MSFC in people with RRMS who received AHSCT, compared with those who remained on DMTs. Two studies compared the change in MSFC from baseline. One found statistically significant improvement for the first three-years post-AHSCT, and no significant difference at four years post-AHSCT (Nash et al. 2017). The second study found a statistically significant improvement throughout four years of reporting post-AHSCT (Burt et al. 2015).

Three studies reported results of the nine-hole peg test (Burt et al. 2019, Nash et al. 2017, Burt et al. 2009). The MIST RCT reported a significant improvement when comparing RRMS patients who had AHSCT with those who remained on DMTs ($p < 0.001$) (Burt et al. 2019).

Three studies reported PASAT (Burt et al. 2019, Burt et al. 2009, Nash et al. 2017). When comparing RRMS patients who had AHSCT with those who remained on DMTs, the difference between the groups in PASAT scores at one-year post-AHSCT was not statistically significant (Burt et al. 2019). Burt et al. (2009) and Nash et al. (2017) measured the change in PASAT from baseline.

Fatigue (measured using the Modified Fatigue Impact Scale) is not frequently reported in the literature however it was found to have decreased at 36 months post-AHSCT with the difference being statistically significant ($p = 0.001$) (Bose et al. 2019).

Three studies reported deaths occurring during their study. Krasulova et al. (2010) reported two deaths, Mancardi et al. (2012) reported three deaths and Muraro et al. (2017b) reported 37 deaths. It is important to point out that Muraro et al. (2017b) was a large retrospective cohort study with long term observational follow-up in which variability existed for both the patient population and conditioning regimen. TRM occurred in three of the 19 studies. Mancardi et al. (2012) reported two TRM, Atkins et al. (2016) reported one TRM and Muraro et al. (2017b) reported eight TRM. Two studies did not report on death or TRM (Bose et al. 2019, Mehra et al. 2019). Overall survival was reported by five studies, ranging between 86.3 and 100%, for which the timeframes ranged between 62 days to 5.2 years post-AHSCT (Burt et al. 2019, Ruiz-Arguelles et al. 2019, Muraro et al. 2017b, Nash et al. 2017, Atkins et al. 2016).

Lesion number, as measured by MRI, was variable across reported studies. Burt et al. (2015) found lesion number decreased (pre-AHSCT to five-years post-AHSCT, $p < 0.001$). Two other studies found no new lesions in its patient population either five-years post-AHSCT or up to 13 years post-AHSCT (range 3.9 to 12.7) (Comini-Frota et al. 2019, Atkins et al. 2016). Three studies found lesion number increased in a proportion of patients. Nash et al. (2017) recorded new lesions in two patients ($n = 24$, RRMS population), Kvistad et al. (2019) recorded new lesions in three patients ($n = 30$, RRMS population), with two of the three patients having experienced clinical relapse and Frau et al. (2018) recorded new lesions in six patients. MRI activity free survival at five-years post-AHSCT was similar in the two studies that reported it, 85% and 86.3% (Nash et al. 2017, Burman et al. 2014); one of these studies reported on an RRMS patient population (Nash et al. 2017). Boffa et al. (2020) compared MRI activity free survival between AHSCT and alemtuzumab treated patients (non-randomised), finding the difference between the treatment groups to be statistically significant ($p = 0.009$). Lesion volume, as measured by MRI, decreased within the two studies that reported it (Burt et al. 2019, Burt et al. 2015). The MIST RCT reported difference in means from baseline to one-year post-AHSCT for RRMS patients who either received AHSCT or remained on DMTs (Burt et al. 2019). Over this time, lesion volume decreased for the AHSCT group

while it increased for the DMT group. The mean difference between the groups was -66 and the comparison was statistically significant ($p < 0.001$).

6.2 Quality of Life outcomes

We identified four studies that measured changes in quality of life (QoL). The studies used various tools to measure QoL:

- Short Form 36 QoL score (SF-36)
- 29-item Multiple Sclerosis Impact Scale (MSIS-29)
- Multiple Sclerosis QoL-54 instrument (MSQoL-54)

QoL outcomes are presented in Table 2. Two studies reported quality of life measured using SF-36. The MIST RCT reported a statistically significant improvement in SF-36 in RRMS patients who had AHSCT compared with those who remained on DMTs ($p < 0.001$). (Burt et al. 2019). The second study reported a statistically significant improvement in SF-36 from baseline ($p < 0.001$) (Burt et al. 2015).

Statistically significant improvement in MSIS-29 from baseline was reported within the first three-years post-AHSCT, but not at year four post-AHSCT (Nash et al. 2017).

Moore (2019) reported MSQoL-54 scores for two domains, physical and mental health, and for both RRMS patients and SPMS patients. For both physical and mental health domains, scores statistically significantly improved for RRMS patients at six-months, one-, two- and three-years post-AHSCT. For SPMS patients, scores statistically significantly improved within the physical health domain at six-months and one-year post-AHSCT only and within the mental health domain at the three-years post-AHSCT time point only.

Table 2. AHSCT – Quality of Life outcomes

Study	RRMS participants (of total)	Outcomes
SF-36		
(Burt et al. 2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	Mean totals increase from 50.5 at baseline to 67.9 at six months and 70.3 at one-year post-AHSCT for AHSCT group compared with decrease from 49.5 at baseline to 45.2 at six months and 46.1 at one-year post-AHSCT for DMT group. Compared with DMT, the increase was statistically significant for AHSCT group ($p < 0.001$)
Burt et al. (2015)	N = 123 (151)	Total median increase from 45 (range 32 to 59.7) to 64 (range 48.1 to 81.3) ($p < 0.001$)
MSQoL-54		
Moore et al. (2019)	N = 20 (35)	Physical health domain: scores statistically significantly improved from baseline at six-months ($p < 0.001$), one-year ($p < 0.001$), two-years ($p < 0.01$), and three-years ($p < 0.05$) post-AHSCT for RRMS patients. Scores statistically significantly improved from baseline at six-months ($p < 0.05$) and one-year ($p < 0.05$) post-AHSCT only for SPMS patients Mental health domain: scores statistically significantly improved from baseline at six-months ($p < 0.01$), one-year ($p < 0.001$), two-years ($p < 0.05$), and three-years ($p < 0.01$) post-AHSCT for RRMS patients. Scores statistically significantly improved from baseline at three-years ($p < 0.05$) post-AHSCT only for SPMS patients

MSIS-29		
Nash et al. (2017)	N= 18 (year 3) N=17 (year 4)	At 3 years, statistically significant improvement in MSIS-29 from baseline was reported. There was a non-significant trend towards improvement at year 4.
AHSCT: autologous haematopoietic stem cell transplant; DMT: disease modifying therapy; MSIS-29: Multiple Sclerosis Impact Scale; MSQol-54: Multiple Sclerosis QoL-54 instrument; RRMS: relapsing remitting multiple sclerosis; SF-36: Short Form 36 QoL score; SPMS: secondary progressive multiple sclerosis		

6.3 Safety

Adverse events of AHSCT are influenced by the intensity of the procedure, particularly the conditioning regimen used (Muraro et al. 2017a). The health of the patient, their age and whether they have comorbidities also plays a role. Across the primary studies from four included systematic reviews and the additional ten primary studies, 19 studies reported adverse events. These are detailed in Table 3. Reported adverse events were mainly transplantation-related (including conditioning regimen-related) and most frequently reported according to the National Cancer Institute's Common Toxicity Criteria. Some studies reported adverse effects according to whether they were early (typically within the first 100 days post-AHSCT) or late (after the first 100 days post-AHSCT). More commonly reported events included febrile neutropenia; diarrhoea; sepsis; urinary tract infections and virus reactivation. Conditioning regimen related and transplantation related events included fever associated with ATG, engraftment syndrome and events associated with acute toxicity such as alopecia, anaemia, thrombocytopenia and leukopenia. Commonly reported late events included virus reactivation and autoimmune thyroid disease; malignancy was less common.

Table 3. AHSCT – safety

Study	RRMS participants (of total)	Adverse events
Boffa et al. (2020)	N = 25 AHSCT N = 32 alemtuzumab	For AHSCT group: early post-AHSCT effects included neutropenic fever (n = 16), sepsis (n = 8) and infusion related reactions (n = 8). Late post-AHSCT effects included viral reactivations (n = 4) and various autoimmune disorders (n = 3). For DMT group: adverse effects mostly included various autoimmune disorders (n = 14) but also infections such as neutropenic fever (n = 1) and pneumonia (n = 2), as well as viral reactivations (n = 3).
Tolf et al. (2019)	N = 10	Early post-AHSCT effects included infections such as neutropenic fever and sepsis as well as serum sickness and nausea (n = 19 recorded). Late post-AHSCT effects included premature menopause, extra-uterine pregnancy, infection and bipolar disorder (n = 4 recorded).
Kvistad et al. (2019)	N = 30	Early post-AHSCT effects included back pain, diarrhoea and infections such as neutropenic fever. 77% of patients had platelet transfusions and 47% had blood transfusions during this time. Late post-AHSCT effects included persisting amenorrhea and autoimmune diseases.
Burt et al. (2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	For AHSCT group: no WHO grade 4 toxicities were reported, no non-haematopoietic toxicities, no transfer to intensive care unit, no parenteral nutrition, no surgery, no other disabling or potential life-threatening events. There were 72 grade 3 toxicities reported, the largest number of these related to hypophosphatemia (n = 17), febrile neutropenia (n = 13), hypokalaemia (n = 13), hyperglycaemia (n = 5), elevated transaminases (n = 5) and hypertension (n = 3). Post-AHSCT infections included upper respiratory tract (n = 16), varicella zoster reactivations (n = 7), urinary tract (n = 6), *C.* difficule diarrhoea (n = 2). For DMT group: infections included upper respiratory tract (n = 15), urinary tract (n = 8) and varicella zoster reactivations (n = 2).
Moore et al. (2019)	N = 20 (35)	Serum sickness associated with ATG (n = 22) was the most frequently reported SAE. There were 29 World Health Organisation grade 3 toxicities reported, the largest number of these related to viral infection (n = 13) specifically shingles (n = 4).
Frau et al. (2018)	N = 5 (9)	Adverse events included *Candida* albicans infection (n = 1), reaction to ATG (n = 1), benign neoplasm 30 months post-AHSCT (n = 1), melanoma three years post-AHSCT (n = 1) and progressive multifocal leukoencephalopathy 12 years post-AHSCT during natalizumab treatment (n = 1)
Muraro et al. (2017b)	N = 46 (281)	Different malignancies (n = 9), specifically myelodysplastic syndrome (n = 3), and new autoimmune diseases (n = 14), specifically autoimmune thyroid disease (n = 8), were reported.

Study	RRMS participants (of total)	Adverse events
Casanova et al. (2017)	N = 28 (38)	Toxicities were reported for all WHO grades 1 (n = 56), 2 (n = 34), 3 (n = 4) and 4 (n = 4). The largest number of these related to gut toxicity (n = 24), skin toxicity (n = 18), mucositis (n = 17) and hepatic toxicity (n = 15). The WHO grade 3 toxicities involved either the gut or skin while the WHO grade 4 toxicities involved hepatic toxicity. Fever associated with ATG (n = 21) and engraftment syndrome (n = 21) also occurred. Malignancy occurred in the long-term follow-up (n = 3).
Nash et al. (2017)	N = 24 (24)	All patients experienced a WHO grade 4 toxicity with the majority being during the conditioning period up to day 29 post-AHSCT, 92% of participants experienced a WHO grade 3 toxicity during this time. Both toxicity grades, 28% of grade 3 and 90% of grade 4, were mostly haematopoietic or gastrointestinal.
Atkins et al. (2016)	N = 12 (24)	Grade 3 or 4 toxicities were experienced by two patients for which enrolment and AHSCT was postponed while the protocol was reviewed. Grade 2 toxicities (n = 8) and grade 1 toxicities (n = 14) were reported. All patients had febrile neutropenia. Late post-AHSCT viral infections (n = 9), mostly shingles (n = 6), and secondary autoimmune events (n = 6) were reported.
Shevchenko et al. (2015)	N = 43 (99)	No major clinical adverse events observed during mobilisation. Otherwise not reported.
Burt et al. (2015)	N = 123 (151)	No early or late cases of fungal, *Pneumocystis jirovecii*, cytomegalovirus, Epstein-Barr virus or John Cunningham (JC)virus. Late reactivation of dermatomal zoster (n = 4), immune-mediated thrombocytopenia (n = 7), hypo- or hyper-thyroidism (n = 7) was reported post-AHSCT. Malignancy occurred in the long-term follow-up (n = 2).
Burman et al. (2014)	N = 34 (41)	Almost all patients experienced acute toxicity, specifically alopecia, anaemia, thrombocytopenia and leukopenia, during hospitalisation while bacterial infections (n = 22) and febrile neutropenia (n = 17) were the next most reported. Late post-AHSCT effects included reactivation of herpes zoster (n = 8) and thyroid disease (n = 4) but no malignancy was reported.
Mancardi et al. (2012)	N = 33 (74)	Early post-AHSCT effects occurred in 80% of patients with neutropenic fever (70%), sepsis (30%), urinary tract infections (25%), diarrhoea and severe mucositis (15%) being the most common. Reactivation of cytomegalovirus with fever (n = 5) was reported. Late post-AHSCT effects occurred in 5% of patients with recurrent varicella zoster and urinary tract infections the most common.
Krasulova et al. (2010)	N = 11 (26)	Early post-AHSCT effects included diarrhoea (n = 16) febrile neutropenia (n = 14), severe mucositis (n = 11) and sepsis (n = 10). Late post-AHSCT effects included severe sepsis (n = 1), recurrent herpetic infection (n = 1), chronic hepatitis B (n = 1), acquired anti-factor VIII syndrome (n = 1) and glioblastoma multiforme (n = 1).
Burt et al. (2009)	N = 21	Adverse effects included neutropenic fever (n = 5), transient neurological symptoms manifested as left-sided hypoaesthesia and attributed to filgrastim-related flare (n =1), dermatomal zoster (n = 2), diarrhoea (n = 1) and grade IV thrombocytopenia (n = 2, patients who had received alemtuzumab).
Bose et al. (2019)	N = 12 (23)	NR

Study	RRMS participants (of total)	Adverse events
Ruiz-Arguelles et al. (2019)	N = 259 (617)	Hospitalisations (n = 32) due to neutropenic fever (n = 15), MS flare (n = 6), pneumothorax (n = 4), persistent nausea/vomiting (n = 3), cardiac arrhythmia (n = 1), rectal bleeding (n = 1), urinary tract infection (n = 1), minimal pleural effusion (n = 1).
Mehra et al. (2019)	N = 22 (36)	No significant adverse effects noted in AHSCT group.
Comini-Frota et al. (2019)	N = 5 (5)	Adverse effects included secondary infection, amenorrhea, alopecia and permanent infertility.
AHSCT: Autologous haematopoietic stem cell transplant; ATG: anti-thymocyte globulin; DMT: disease modifying therapy; JC: John Cunningham virus; SAE: serious adverse event; WHO: World Health Organisation		

6.4 Ongoing studies

We identified six ongoing studies, the details of which are outlined in Table 4.

Table 4. Ongoing studies

Study	Sites Identifier	Number of patients	Estimated primary completion date	Primary outcome
Outpatient Hematopoietic Grafting in Patients With Multiple Sclerosis Employing Autologous Non-cryopreserved Peripheral Blood Stem Cells: A Feasibility Study	Single-centre, Mexico NCT02674217	1000	December 2020	Patient-reported EDSS over four years
Randomized Autologous Hematopoietic Stem Cell Transplantation Versus Alemtuzumab for Patients With Relapsing Remitting Multiple Sclerosis (RAM-MS)	Denmark, Netherlands, Norway and Sweden NCT03477500	100	March 2022	Proportion of patients with no evidence of disease activity over two years (with five-year planned extension)
Maximizing Outcome of Multiple Sclerosis Transplantation: "MOST" Trial	Single-centre, USA NCT03342638	200	January 2023	Efficacy – rate of disease activity over five years
A Multicentre Randomized Controlled Trial of Best Available Therapy Versus Autologous Hematopoietic Stem Cell Transplant for Treatment-Resistant Relapsing Multiple Sclerosis (ITN077AI), also known as BEAT-MS	USA, UK NCT04047628	156	December 2025	Multiple Sclerosis Relapse Free Survival over three years (from randomisation)
Autologous stem cell transplantation versus alemtuzumab or ocrelizumab in relapsing remitting multiple sclerosis (STAR-MS)	Multicentre, UK NA	198	July 2024	No evidence of disease activity over two years
Autologous Haematopoietic Stem Cell Transplantation for highly active treatment resistant multiple sclerosis	Single-centre, Australia ACTRN12619000348156	50	NR	Safety as measured by TRM at day 100. Efficacy as measured by mean time to first relapse, mean time to three and six month sustained change in EDSS and mean ARR in MS refractory to DMTs

Open study of autologous hematopoietic stem cell transplantation in patients with RRMS and progressive forms of MS (5 year duration)	Single-centre, Switzerland NA	NR	NR	NR
A randomised controlled trial to Compare Ocrelizumab or Alemtuzumab with autologous Hematopoietic Stem Cell Transplantation (aHSCT) in high inflammatory Multiple Sclerosis (COAST)	Unclear, Germany EduraCT Number: 2016-001166-29	50	NR	NEDA at two years
No Evidence Of Disease Activity After Autologous Haematopoietic Stem Cell Transplantation In Aggressive Multiple Sclerosis	Unclear, Italy NA	90	NR	NEDA at three years

AHSCT: autologous haematopoietic stem cell transplant; EDSS: expanded disability status scale; NEDA: no evidence of disease activity; NR: not reported; TRM: transplant-related mortality

7. Economic evaluation

7.1 Health economic evidence review

This EAR was adapted from the advice statement produced by SHTG, which found no relevant and peer-reviewed studies investigating the cost effectiveness of AHSCT in patients with highly active RRMS not responding to high-efficacy DMTs. HTW researchers ran an update of the SHTG search. Two potentially relevant health economic studies were identified in the search. One was excluded as it was a literature review (Dunn-Pirio et al. 2019), while the second study was not an health economic evaluation, but was instead included in the review of the clinical effectiveness of AHSCT (Tappenden et al. 2019).

The literature review by (Dunn-Pirio et al. 2019) included a further potentially relevant UK health economic evaluation. The study examined the cost effectiveness of AHSCT versus mitoxantrone in people with SPMS and so was not deemed to be applicable to the population considered in this EAR (Tappenden et al. 2010).

7.2 Original health economic analysis

The review of the clinical effectiveness evidence for this question, based on an update of the search originally undertaken by SHTG, found no additional RCTs published since the SHTG advice statement (SHTG 2019). While further observational studies were identified and included in the evidence review, the MIST RCT represents the highest level of clinical evidence currently available (Burt et al. 2019). Therefore, an economic analysis was undertaken using clinical data from the MIST RCT.

A cost utility analysis was undertaken to determine the cost effectiveness of AHSCT compared with DMTs for people with RRMS. A Markov model was used to estimate costs and quality-adjusted life years (QALYs) over a five year time horizon, from the UK NHS and personal social services perspective. Costs and QALYs were discounted at 3.5% per year as recommended in the NICE reference case. The methods, results and discussion are provided in full in appendix 6 of this report.

Key details and results of the analysis are summarised in table 5. AHSCT was found to be dominant (more effective and less costly than DMTs) in most modelled scenarios. The notable exceptions were the scenarios which combined an assumption that no improvements in EDSS are permitted after year one and an assumption that people progressing to EDSS 2 receive DMT rescue. In these scenarios, AHSCT was still found to be more effective but it was also found to be more costly. When compared against all DMTs, the ICER was found to be £38,359 per QALY gained indicating that AHSCT was not cost-effective as the ICER was above the threshold of £20,000 per QALY gained. When compared against natalizumab only, the ICER was found to be £2,741 per QALY gained indicating that AHSCT was cost-effective as the ICER was below the threshold of £20,000 per QALY gained.

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The model is run 10,000 times. At a threshold of £20,000 per QALY, AHSCT was found to have a 100% probability of being cost-effective while standard care with DMTs had a 0% probability of being cost-effective.

Table 5. Summary of cost utility analysis

Study details	Data sources	Results (per person)	Limitations
Type of economic analysis: Cost Utility Analysis (cost per QALY gained) Population: People with relapsing-remitting MS who experienced at least 2 relapses while receiving DMT in the prior year, and with an EDSS score of 2.0 to 6.0 Intervention: AHSCT Comparator: Basket of DMTs used in MIST RCT Perspective: UK NHS Currency: UK pound sterling (£) Price year: 2018/2019 Time horizon: 5 years Discounting (costs/outcomes): 3.5%/3.5% Conflict of interest: None	Design: Markov model comprising 11 health states representing EDSS 1.0 to EDSS 10 (death, all causes), one year cycle length Source of baseline and effectiveness data: Hazard ratio for disease progression from MIST RCT applied to rates of disease progression reported in Hettle et al. (2018). Baseline EDSS from MIST RCT. Acute relapse rate from MIST RCT. Source of resource use and cost data: Resource use not reported in MIST RCT, so resource use estimated by clinical experts. Cost items: Harvesting, transplant and monitoring costs of AHSCT, acquisition, administration and monitoring costs of DMTs, SPMS management, costs of managing acute relapse, EDSS-specific costs. Cost sources: NHS Reference Costs (2018/2019), British National Formulary(Joint Formulary Committee 2020), Hettle et al. (2018) Source of utility data: EDSS-specific utilities from Orme et al. (2007), obtained using EQ-5D with UK valuation.	1. Base Case: Total costs DMT: £73,496 AHSCT: £31,087 Incremental: Saves £42,409 Total QALYs DMT: 2.94 AHSCT 3.15 Incremental: 0.21 ICER (deterministic): Dominant Probability cost effective at £20,000 per QALY gained threshold (probabilistic; 10,000 runs): 100% Deterministic sensitivity analyses 2. AHSCT versus Natalizumab only ICER: AHSCT dominant 3. DMT rescue in AHSCT arm after progression to EDSS 2 ICER: AHSCT dominant 4. AHSCT versus Natalizumab with DMT rescue in AHSCT arm after progression to EDSS 2 ICER: AHSCT dominant 5. No improvements in EDSS permitted within transition probabilities ICER: AHSCT dominant Combining 3. And 5. ICER: £38,359 Combining 4. And 5. ICER: £2,741	Limitations • Analysis was based on the MIST RCT only and so shares its limitations • Since MIST RCT, experts advise the use of injectables interferon/glatiramer is decreasing in first line. This might decrease the costs of DMTs. • High efficacy DMTs ocrelizumab and alemtuzumab not included in the MIST RCT and model • No adverse events included in model • Data on effectiveness of DMTs includes some people managed with mitoxantrone which is not used in the UK. • Discontinuation from DMTs not modelled. • People with SPMS all managed with interferon in AHSCT arm, while 50% assumed to not receive SPMS diagnosis in DMT arm (with exception of scenarios where rescue therapy with DMTs is introduced post-transplant) • One relapse per year in people who experience relapse. Same relapse rate applied in EDSS 0-6 (constant over time)

AHSCT: Autologous Haematopoietic Stem Cell Transplant; EDSS: Expanded Disability Status Scale; EQ-5D: EuroQoL 5 Dimensions; DMTs: Disease Modifying Therapies; ICER: Incremental Cost Effectiveness Ratio; MIST: Multiple Sclerosis International Stem Cell Transplant Trial; MS: Multiple Sclerosis; QALY: Quality Adjusted Life Years; RCT: Randomised Controlled Trial; SPMS: Secondary Progressive Multiple Sclerosis

7.3 Resource impact analysis

The population that may receive AHSCT was estimated based upon expert opinion on the number of people with RRMS that may be eligible for treatment (i.e. people whose disease is inadequately controlled despite high efficacy DMTs). Representatives from Cwm Taf Morgannwg, Cardiff and Vale, Swansea Bay and Hywel Dda University Health Boards each estimated that 1-5 patients within their catchment area would be eligible for treatment with AHSCT per year. Assuming that an equivalent rate would be observed in the other Health Boards in Wales, it was estimated that there may be 7-37 patients eligible for treatment with AHSCT per year. The analysis was based upon the midpoint estimate of 22 patients but results are also presented for the upper and lower estimates.

The unit costs specified in the cost-utility analysis section were applied in the budget impact analysis. Thus, a total cost of £25,470 was applied for an AHSCT procedure while one year of DMT treatment was estimated to cost £14,484 in year one and £14,144 in subsequent years (see table 14, table 15 and table 16 in appendix 6 for details). The costs for the management of an acute relapse and subsequent management based on EDSS scores, including progression to SPMS, were also based on costs from the cost-utility analysis (see table 16 and table 17 in appendix 7 for details). Rates of relapse and progression following treatment were informed from clinical inputs applied in the cost-utility analysis.

The results of the resource impact analysis are shown in table 6. It can be seen that the initial treatment cost with AHSCT was estimated to be much higher than the initial treatment cost with DMTs (estimated cost increase of £241,863). However, the initial cost was offset by savings accrued in subsequent years through a reduction in the cost of disease management. In year one, it can be seen that AHSCT has a net cost impact of £235,669 but from year two onwards, AHSCT was estimated to result in overall net savings. At year five, AHSCT was estimated to result in net savings of £990,389 (ranging from £330,130 to £1,650,649 using lower and upper population estimates).

Table 6: Resource impact for estimated population with RRMS in Wales that would be eligible for AHSCT treatment (n=22)

Cost items	Standard care	AHSCT	Difference in cost element	Net impact of AHSCT
Initial treatment cost	£316,489	£558,352	£241,863	-
Subsequent disease management costs*				
Year 1	£25,474	£19,280	-£6,194	£235,669
Year 2	£334,420	£26,977	-£307,443	-£71,774
Year 3	£334,114	£27,216	-£306,898	-£378,672
Year 4	£333,687	£27,454	-£306,233	-£684,905
Year 5	£333,168	£27,683	-£305,484	-£990,389
*Subsequent management costs include the cost of further DMT treatment, management costs based on EDSS scores, management costs for acute relapses and AHSCT follow-up appointments				
AHSCT: Autologous haematopoietic stem cell transplant; DMT: disease modifying therapy; EDSS: expanded disability status scale				

8. Organisational issues

AHSCT for previously treated RRMS is not provided through NHS Wales. According to the NHS Commissioning Board in England, AHSCT is a clinical option and can be considered after assessment of risks and benefits, as per British Society of Blood and Marrow Transplantation recommendations, for severe, resistant MS. WHSSC have recently published a policy position extending NHS Wales funding to include severe, resistant MS, where all patients must be deemed to have severe treatment resistant disease and be sufficiently fit for transplant procedure as determined by appropriate multi-specialty review (WHSSC 2020a). Access for Welsh patients has been through private care up until this point, usually from overseas providers (Expert Comments, 30 December 2019, 10 January 2020, 20 February 2020). Clinical experts consulted by HTW anticipate that there would be a very small number of Welsh-based MS patients who may fulfil criteria for AHSCT every year, however, experts with direct experience of carrying out this procedure for MS patients consider these numbers to be an underestimate of those who could benefit (Expert Comments, 30 December 2019, 09 January 2020, 17 February 2020, 25 February 2020). All clinical experts agreed on the importance of AHSCT being available as a treatment for MS within Wales but, as it becomes available, many also indicated the need for input from units with expertise of this treatment in other parts of the UK (Expert Comments, 14 February 2020, 17 February 2020, 17 February 2020, 20 February 2020, 25 February 2020, 6 March 2020, 16 March 2020). There was agreement amongst clinical experts that, although potentially difficult, a guideline, to standardise AHSCT as a treatment for MS in Wales, should be developed as it becomes available (Expert Comments, 14 February 2020, 17 February 2020, 17 February 2020, 20 February 2020, 25 February 2020, 6 March 2020, 16 March 2020). There were suggestions that a Welsh guideline should harmonise with guidelines already being used within the UK, thus supporting the established trial network and also ensuring that the roles of multi-disciplinary team members are clearly outlined (Expert Comments, 17 February 2020, 20 February 2020). A few clinical experts highlighted the importance of Welsh engagement with the ongoing UK-wide STAR-MS trial (see table 4, section 6.4 ongoing studies), for both potential patients and future policy (Expert Comments, 17 February 2020, 16 March 2020). Alongside the introduction of ASHCT for MS in Wales, the establishment of an all Wales, multicentre, multidisciplinary panel of experts to screen referred patients for AHSCT would ensure objective, consistent decision making (Expert Comments, 14 February 2020, 17 February 2020, 20 February 2020, 25 February 2020, 6 March 2020, 16 March 2020).

Guidelines have recommended a close collaboration between AHSCT specialists and MS specialists at transplant units where MS patients may receive AHSCT (Sharrack et al. 2019, NHS England 2019, SHTG 2019, Das et al. 2019). Guidelines have also recommended that transplant units should be accredited by either the Joint Accreditation Committee of the International Society for Cellular Therapy and EBMT (JACIE) or an equivalent organisation (Sharrack et al. 2019, SHTG 2019, Das et al. 2019). As of January 2020, there is one JACIE accredited centre in Wales, the North Wales Stem Cell Transplant Programme based at Ysbyty Gwynedd Bangor (EBMT 2020b). A second centre is seeking JACIE re-accreditation, the South Wales Blood and Marrow Transplant Programme based at University Hospital of Wales, Cardiff and Vale University Health Board and Singleton Hospital, Abertawe Bro Morgannwg University Health Board (EBMT 2020a).

Six providers of AHSCT for Welsh adults have been named within a recently published specialised services service specification document supporting the WHSSC policy position, four of which are in England (WHSSC 2020b). The barriers to delivering this care in Wales include the lack of accredited transplant units where collaborative multi-disciplinary teams exist between AHSCT specialist teams and MS specialist teams (Das et al. 2019). Delivery of AHSCT for MS in Wales would require the development of specialist MS-AHSCT teams with adequate training. There were likely be a learning curve for the teams, as experienced transplant units have the most promising outcomes (Expert Comments, 17 February 2020, 20 February 2020, 25 February 2020, 6 March

2020, 16 March 2020). Any under-capacities in transplant or MRI facilities (supporting clinical trial outcomes measurement), consultant staff for service delivery or day case infusion units would adversely impact delivery of this care (Expert Comment, 16 March 2020). The availability of neuro-rehabilitation and support services including physiotherapy, psychology and occupational therapy services would be essential for patients to maximise the benefits of the treatment (Expert Comments, 17 February 2020, 20 February 2020). Adverse effects of AHSCT experienced by MS patients would be different from patients with haematological disorders, further necessitating specialist training for existing centres (Expert Comment, 14 February 2020). There may be regulatory issues relating to the medicines used for conditioning regimens, as none of them are licensed for this use (NICE 2018). If provided in Wales, MS patients would be able to access care at specialist units without traveling abroad, allowing Welsh-based patients to have equity of treatment and, ideally, a reduction in variation of that treatment.

9. Patient issues

9.1 Patient issues from literature search

Our literature search identified research on patient experiences from five studies, four of which have been described above (Kvistad et al. 2019, Ruiz-Arguelles et al. 2019, Bose et al. 2019, Atkins et al. 2016). Bose et al. (2019) and Atkins et al. (2016) reported on the same trial.

Kvistad et al. (2019) recorded working status of patients' pre-AHSCT and post-AHSCT in this retrospective study. Before AHSCT treatment, only one patient was working full-time and five were receiving disability benefits (n = 30). After AHSCT treatment, ten patients started working full-time.

Ruiz-Arguelles et al. (2019) is a feasibility study which considers patients' self-reported EDSS (n = 240 at one-year post-AHSCT). EDSS is usually measured by a patient's neurologist but in this study, patients were instructed to provide information on their neurological status and adverse events every three months post-AHSCT via special forms submitted electronically. At one-year post-AHSCT, 47% reported improvement in EDSS and 31% reported stabilisation in EDSS. EDSS was assessed at 3, 6, 9, 12, and 15 months post-AHSCT and was found to decrease from a mean of 5.1 to a mean of 4.5 ($p = 0.0002$). EDSS response rate (improvement plus stabilisation) was 83% in RRMS, 78% in PPMS and 73% in SPMS patients (Ruiz-Arguelles et al. 2019).

Bose et al. (2019) analysed the association between fatigue impact scale scores post-AHSCT and changes in social wellbeing such as employment, driving status and relationship status (n = 23). At the end of the trial, employed patients had a median modified fatigue impact scale (mFIS) of 16 while unemployed patients had a median mFIS of 32 ($p = 0.023$). Of those patients with absolute change in mFIS of ‹ 38 (n = 15), 60% were employed (n = 9), 53% were driving (n = 8) and 73% were in a relationship (n = 11) at the end of the study period. Of those patients with absolute change in mFIS of › 38 (n = 8), 12.5% were employed (n = 1), 37.5% were driving (n = 3) and 62.5% were in a relationship (n = 5) at the end of the study period. There was no statistical analysis related to these changes.

Atkins et al. (2016) analysed social well-being post-AHSCT (n = 23) through working status or school attendance, receipt of long-term disability benefits; relationship status, and possession of a driver's licence. No statistical analyses were carried out for these outcomes. Patients were categorised according to evidence of sustained accumulation of disability following AHSCT (n = 7) and NEDA following AHSCT (n = 16), so the groups were weighted unevenly. Post-AHSCT, there was a greater percentage of patients with NEDA working or attending school (56%) compared with those with evidence of sustained accumulation of disability (14%). More people

with NEDA were married, engaged or in a common-law partnership (81%) compared with 43% in people with sustained accumulation of disability. Similarly, more people with NEDA held a driver's licence (69%) compared with patients with evidence of sustained accumulation of disability (0%). Specifically, five patients got married or engaged and two had children using previously banked or donated gametes.

De Kleermaeker et al. (2019) aimed to evaluate participants' knowledge and expectations of AHSCT and their actual and desired sources of information by questionnaire in a study based in the Netherlands (n = 137). Participants (mainly patients on natalizumab) were recruited at an outpatient facility and day care unit in Amsterdam. Of those taking part (n = 113), median age was 41 years (range 20 to 66 years), participants mostly had RRMS (74%), median disease duration was 8 years (range 0 to 28 years) and median estimated EDSS was 4 (range 0 to 8). The study was limited as the questionnaire was not formally validated and disease history was self-reported. Many participants reported being on second line treatment, which may equate to more active MS and more regular treatment, which may result in increased knowledge and awareness of treatment options. The authors also acknowledged that the sample population is unlikely to be representative of the MS population in the Netherlands.

Perceived knowledge about MS therapies was much better for DMTs than for AHSCT, with approximately 50% of participants rating their level of knowledge on DMTs as sufficient while only 25% of participants rated their knowledge on AHSCT as such (De Kleermaeker et al. 2019). Just over half of the participants (56%) reported that they were satisfied with their current treatment. In terms of the effect of AHSCT, most participants (79%) expected no more disability progression post-AHSCT while approximately 20% expect disability progression to continue but at a slower pace. Most participants expected to have either no more relapses (55%) or for relapses to be partially prevented (41%) post-AHSCT. Participants also believed that AHSCT was either most likely to be more effective than highly effective DMTs (50%) or that there was insufficient evidence on the effectiveness (44%). Only 45% of participants were able to mention at least one possible side effect of AHSCT with increased risk of infection (28%) and death (10%) being most frequently mentioned. Most participants (70%) did feel they needed more information on AHSCT, however, only 25% actively sought such information. When asked whether they wanted AHSCT, 19% wanted it at that moment while 54% would consider it as a future treatment. Specifically, participants with a shorter disease duration (≤ 10 years) and more disability (EDSS › 3.5) and dissatisfaction with their current treatment were more likely to want AHSCT at that moment or possibly in the future. Almost 80% of patients believed their country (the Netherlands) should offer AHSCT to participants and the same proportion believed that their neurologist was not influenced by industry (De Kleermaeker et al. 2019).

9.2 Patient and public involvement

HTW routinely considers patient perspectives identified as part of reviewing the literature search for clinical and cost-effectiveness; this is reported in section 9.1. In addition, HTW is committed to establishing effective patient and public involvement (PPI) and therefore considers a number of PPI mechanisms, tailoring the approach accordingly. The appropriate mechanism(s) are determined based on input from the PPI Standing Group, who advise HTW on best practice and topic-specific issues. For this topic, HTW invited submissions from patient organisations and received evidence from the MS Trust and MS Society Cymru. This information remains confidential, but was considered by Committee members.

10. Conclusions

This review identified evidence relating to AHSCT to treat people with previously treated RRMS. The treatment protocols (specifically conditioning regimens) and patient populations varied greatly across the studies.

Overall, the published evidence showed that AHSCT has the potential to improve the condition. The current evidence is limited. The majority of studies were uncontrolled, observational case series. Reported outcomes varied across all studies (and were not defined for some studies) and outcomes were usually not measured over long timeframes. There are certain outcomes, such as NEDA, which are more frequently being considered to be more valuable indicators of treatment efficacy, however, up until recently, these indicators were not widely measured within clinical studies. The evidence was limited also in terms of study inclusion criteria. There was variation in how MS clinical types were defined and most studies had mixed patient populations. Adverse events reported in the studies were common and included pre-AHSCT (conditioning regimen related) and post-AHSCT effects, the latter of which included both short- (febrile neutropenia) and long-term (autoimmune thyroid disease) effects. Five studies were included which considered patient experience with AHSCT, with two studies reporting on the same trial. The studies reported on a mix of outcomes.

The review of the clinical effectiveness evidence for this question did not identify any additional RCTs published since the MIST RCT, which was identified in the advice statement produced by SHTG (SHTG 2019). HTW researchers based an original cost-utility analysis on the MIST RCT. The results find that AHSCT is dominant (more effective and less costly) over the DMTs in the MIST RCT in people with highly active RRMS. At a threshold of £20,000 per QALY gained, AHSCT was found to have a 100% probability of being cost-effective while standard care with DMTs had a 0% probability of being cost-effective. This result is explained by the high ongoing costs of DMTs compared with the up-front cost of AHSCT, combined with the high effectiveness of AHSCT as reported in the MIST RCT. In a scenario where AHSCT is compared with the higher efficacy DMT natalizumab, the result does not change and AHSCT remains dominant. AHSCT remains dominant because, despite being more effective relative to other DMTs, natalizumab is also more costly than other DMTs.

11. Further research

More evidence generated through randomised controlled trials, within an RRMS patient population and using appropriate high efficacy DMTs as comparators is warranted. This research gap will be addressed by ongoing RCTs including the UK-based STAR-MS RCT, which will compare AHSCT with alemtuxumab or ocrelizumab. More reporting on patient experience evidence is also warranted.

12. Contributors

This topic was proposed by Andrew Champion, Assistant Director, Evidence Evaluation and Effectiveness, WHSSC.

The HTW staff and contract researchers involved in writing this report were:

- J Washington – literature search
- B Kenny – clinical author
- S Hughes – health economics author
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- L Elston – clinical research support
- A Evans – PPI
- A Mironas- clinical quality assurance check
- M Prettyjohns- health economics quality assurance check
- S McAllister – project management

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

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Appendix 1. Glossary

ABN	The Association of British Neurologists
AHSCT	autologous haematopoietic stem cell transplantation
ARR	annualised relapse rate
ATG	anti-thymocyte globulin
BCNU	bis-chloroethylnitrosourea, also known as carmustine
BEAM	BCNU, etoposide, cytarabine/cytosine-arabinoside, melphalan
CC	casemix companion split
CEAC	cost effectiveness acceptability
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
Cyc	cyclophosphamide
DMTs	disease modifying therapies
EAR	evidence appraisal report
EBMT	European Society for Blood and Marrow Transplantation
EBV	Epstein-Barr virus
EDSS	expanded disability status scale
FIS	fatigue impact scale
G-CSF	granulocyte-colony stimulating factor
Gd	gadolinium
HA-RRMS	highly active relapsing remitting multiple sclerosis
HRG	Healthcare Resource Group
HSC	haematopoietic stem cell
HTW	Health Technology Wales
ICER	incremental cost effectiveness ratio
JACIE	Joint Accreditation Committee of the International Society for Cellular Therapy and EBMT
JC virus	John Cunningham virus (also known as human polyomavirus 2)
MDTs	multi-disciplinary teams
MIST	Multiple Sclerosis International Stem Cell Transplant Trial
MRI	magnetic resonance imaging
MS	multiple sclerosis

MSSS	MS severity score
NEDA	no evidence of disease activity
NICE	National Institute for Health and Care Excellence
NR	not reported
NRS	Neurologic Rating Scale
NS	not specified
PFS	progression free survival
PICO	patient intervention comparator outcome
PPMS	primary progressive multiple sclerosis
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
QoL	quality of life
RCT	randomised controlled trial
RES-RRMS	rapidly evolving severe relapsing remitting multiple sclerosis
RFS	relapse free survival
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse events
SHTG	Scottish Health Technologies Group
SPMS	secondary progressive multiple sclerosis
SRD	sustained reduction in disability
TBI	total body irradiation
TER	topic exploration report
TLI	total lymphoid irradiation
TRM	transplant related mortality
WHSSC	Welsh Health Specialised Services Committee

Appendix 2. PICO framework

	Inclusion criteria	Exclusion criteria
Population	People with previously treated/rapidly evolving severe/highly active/refractory relapsing-remitting multiple sclerosis that has not yet become progressive in nature	
Intervention	Autologous haematopoietic stem cell transplantation, immune reconstitution therapy, HSCT, AHSCT. Paired with conditioning regimens which may be myeloablative or non-myeloablative including cyclophosphamide (Cyc)-antithymocyte globulin (ATG) conditioning, BEAM (BCNU/carmustine, etoposide, cytarabine/cytosine-arabinoside and melphalan) conditioning or appropriate modifications of these regimens.	
Comparison/ Comparators	Current treatment practice to be guided by clinical/expert input Alemtuzumab Ocrelizumab Cladribine Fingolimod Natalizumab (if RES-RRMS)	
Outcome measures	Relapse Disease progression (progression-, event- or disease activity-free survival) Expanded disability status scale (EDSS) Other relevant functional scores Lesions in MRI Symptoms of multiple sclerosis Any disability or quality of life outcomes Safety outcomes (adverse events, discontinuations) Mortality Treatment related mortality	
Study design	Randomised or non-randomised trials. We will only report evidence from non-randomised trials for outcomes with no evidence from randomised trials. Economic evaluations	
Search limits	Our search will be limited from the date of the SHTG literature search on the same topic. The SHTG report will be used to identify relevant evidence before April 2019. Only articles published in English will be considered for inclusion.	
Other factors	None.	

Appendix 3. Table 7. Study characteristics

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
Randomised Controlled Trials					
Burt et al. (2019)	Preliminary randomised control trial Median follow-up 24 months (range 12 to 48 months) Multicentre (n = 4), USA, England, Sweden, Brazil clinicaltrials.gov number: NCT00273364	N = 110 (randomised), 103 included in primary analysis N = 52 received AHSCT and included in primary analysis N = 51 received DMT and included in primary analysis Inclusion criteria: RRMS by McDonald criteria, 18-55 years, 2 or more clinical relapses or 1 relapse and MRI gadolinium-enhancing lesion(s) at a separate time within the previous 12 months despite receiving treatment with DMT, EDSS 2.0-6.0 Median age pre-enrolment: 34 (range 18 to 54 years) for AHSCT group (n = 55); 36 (range 19 to 52 years) for DMT group (n = 55) Median MS duration pre-enrolment: 56 (range 9 to 168 months) for AHSCT group (n = 55); 65 (range 8 to 255 months) for DMT group (n = 55) Sex: 38% male, 62% female for AHSCT group (n = 55); 34% male, 66% female for DMT group (n = 55)	Intermediate intensity conditioning: Cyc 50 mg/kg/day from day 5 to 2 ATG 0.5 mg/kg at day -5, 1 mg/kg at day -4, 1.5 mg/kg from day -3 to -1	• Time to disease progression • Survival • Relapses • Neurologic Rating scale • MRI T2 lesion weighted volume • SF36 • MSFC score • 9-hole peg test • PASAT Post-hoc end points included evaluation of time to first relapse in the AHSCT and DMT groups; outcomes in the subset of patients in the DMT group treated with natalizumab; evaluation for NEDA; evaluation of clinical outcomes for patients in the DMT group who crossed over to receive AHSCT; and evaluation of the entire study cohort to assess the effects of disease duration or study site on disease progression.	

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
Applicable primary studies from Zhang & Liu (2020), systematic review and meta-analysis					

Tolf et al. (2019)	Retrospective case series
	
	Follow-up 10 years
	
	Single centre, Sweden
		N = 10
		
		Inclusion criteria: RRMS according to McDonald criteria. Aggressive MS according to criteria proposed by Rush et al.
		
		Median age at AHSCT: 27 years (9 to 33 years)
		
		Median disease duration at AHSCT: 28 months (range 4 to 113 months)
		
		Sex: 30% male, 70% female
			Intermediate intensity conditioning:
			
			BEAM plus ATG (n = 9); BCNU 300 mg/m^2, cytosine arabinoside 800 mg/m^2, etoposide 800 mg/m^2, melphalan 140 mg/m^2 and ATG 6 mg/kg
			
			Cyc plus ATG (n = 1); Cyc 200 mg/kg and ATG 6 mg/kg
				• Sustained complete remission whereby the following criteria are fulfilled for at least a 5 year period:
				  ○ No clinical relapse
				  ○ No EDSS progression
				  ○ No MRI event
				  ○ No ongoing atrophy
				  ○ No DMTs started
				• Resolved MS whereby sustained complete remission present as well as an absence of intrathecal IgG production and no evidence of axonal damage
				• NEDA-3
				• EDSS
					Sustained complete remission similar to NEDA-4

Frau et al. (2018)	Retrospective case series Mean follow-up 13 years (range 11 to 18 years) Singlecentre, Italy	N = 9 RRMS n = 5, SPMS n = 2, PPMS n = 1, n=1 progressive relapsing Inclusion criteria: MS according to diagnostic criteria evolving over time (Poser criteria, McDonald criteria) Mean age at AHSCT: 38 years (SD ± 11.4 years) Mean disease duration at AHSCT: 10 years (SD ± 8 years) Sex: 33% male, 67% female	Intermediate conditioning: BEAM (n = 1); details NR Cyc plus ATG (n = 7); details NR Allogenic AHSCT (n = 1)	• Relapse • Time to first relapse after AHSCT • EDSS • MRI related changes including new lesions and/or enhancing lesions	

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
Applicable primary studies from Ge et al. (2019), systematic review and meta-analysis					
Casanova et al. (2017)	Retrospective case series Median follow-up 8.4 years (range 2 to 16 years), 5.9 years for RRMS and 9.6 years for SPMS Multicentre (n = 2), Spain	N = 38 RRMS n = 28, SPMS n = 10 Inclusion criteria: RRMS or SPMS under treatment with MS-approved drugs for more than one year who had experienced one or more relapses in the previous year and worsening of at least one point in disability (EDSS). Mean (SD) age at AHSCT: 36.7 years (9.1 years) Mean (SD) MS duration at AHSCT: 9.5 years (7.6 years) Sex: 28.9% male; 71.1% female	Intermediate intensity conditioning (BEAM): BCNU 300 mg/m^2 at day -7, cytosine arabinoside 200 mg/m^2 and etoposide 200 mg/m^2 from day -6 to day -3, and melphalan 140 mg/m^2 at day -2.	• Time to first relapse • Time to one-point increase in disability (EDSS) sustained for six months • NEDA (the absence of relapses and/or increases of disability according to the previous definition and no new T2 lesions or gadolinium-enhanced lesion in the MRI performed in the last control) • SRD (the improvement of at least 1.0 point in the EDSS, sustained for 6-months) • Toxicity	This was included in SHTG advice (2019).
Nash et al. (2017)	Prospective, open-label, single-arm, phase II clinical trial Median follow-up 5.2 years (range 1 to 6 years) Multicentre (n = 4), USA clinicaltrials.gov: NCT00288626	N = 24 (RRMS) Inclusion criteria: 18-60 years, MS by McDonald criteria with (1) RRMS; (2) EDSS 3.0 – 5.5 at baseline; (3) Gadolinium enhanced lesions on brain MRI consistent with MS; (4) disease duration < 15 years; and (5) failure of DMT, defined as ≥ 2 clinical relapses over 18 months while on therapy and associated with EDSS increase (by 1.0 for EDSS of 3.0 – 3.5 or by 0.5 for EDSS of 4.0 – 5.5 and sustained ≥ 4 weeks). Mean age at AHSCT: 37 years (range 31 to 42 years) Median MS duration at AHSCT: 4.9 years	Intermediate intensity conditioning (BEAM): BCNU 300 mg/m^2 at day -6, cytosine arabinoside 200 mg/m^2 and etoposide 200 mg/m2 from day -5 to day -2, and melphalan 140 mg/m^2 at day -1.	• Time to treatment failure during five years post-AHSCT meaning death or disease activity. Disease activity included either disability progression (change in EDSS at least six months post-AHSCT of > 0.5 compared to baseline and confirmed three months later), relapse (new neurologic symptoms lasting over 48 hours) or new lesions on MRI (two or more gadolinium- enhancing or new T2-weighted lesions at 1 year or longer after transplant). • MSFC, a multidimensional clinical outcome measure • MSIS-29, a patient-based outcome	This was referred to in SHTG advice (2019) but not included.

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
		Sex: 32% male; 68% female		measure • Toxicity • PASAT-3 • Nine-hole peg test	
Atkins et al. (2016)	Single-arm, phase II trial Median follow-up was 6.7 years (range 3.9 to 12.7 months) Multicentre (n = 3), Canada clinicaltrials.gov: NCT01099930	N = 24 RRMS n = 12, SPMS n = 12 Inclusion criteria: 18-50 years, multiple early relapses, early development of sustained disability (EDSS) specifically affecting motor control with cerebellar or pyramidal KFS scores of at least 3 within 5 years of disease onset, evidence of ongoing clinical disease activity despite at least one year of immune-modulatory/-suppressive treatment, EDSS of 3-6 with a cerebellar or pyramidal KFS of at least 3, and MRI satisfying Paty or Fazekas criteria. Mean age at AHSCT: 34 years (range 24 to 45 years) Mean (SD) MS duration at AHSCT: 6.1 years (2.5) Sex: 42% male; 58% female	High intensity conditioning: Busulfan with monitoring of first dose pharmacokinetics, administered every 6 h for 16 doses from day -10 to -6, Cyc (50 mg/kg per day, intravenously) from day -5 to -2, and ATG (1· 25 mg/kg per day, intravenously) from day -4 to -1.	• MS activity free survival at 3 years post-AHSCT. Events were defined as clinical relapse, appearance of new lesions on MRI or sustained progression of EDSS. • Time to treatment failure (relapse or progression) • Overall survival • Transplantation related mortality • Transplantation related morbidity • Immunological reconstitution • Haematopoietic reconstitution • MRI related changes including new lesions and atrophy	This study was built upon and published by Bose et al. (2019). First 12 patients enrolled had higher EDSS, further from diagnosis but still having relapses. These patients were more likely SPMS (n = 11).
Shevchenko et al. (2015)	Prospective long-term study Median follow-up was 4.1 years Single centre, Russia	N = 99 RRMS n = 43, SPMS n = 35, PPMS n = 18, PRMS n = 3	Intermediate intensity conditioning (modified BEAM): BCNU/CCNU 300 mg/m^2 melphalan 50-100 mg/m^2 (n = 60)	• Event-free survival	Outcomes not defined, conditioning treatments had by different patients not defined.

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
		Inclusion criteria: 18-55 years, MS by McDonald criteria. EDSS 1.5-8, normal mental status, absence of severe concomitant diseases, +/- Gd-lesions and no treatment with interferons or immunosuppressive agents within 3 months of enrolment. Mean age at AHSCT: 34.6 years; RRMS 32.7 years Median MS duration at AHSCT: 5 years (range 0.5 to 24 years); for RRMS 4 years (range 0.5 to 10 years) Sex: 39.1% males, 60.1% female; RRMS 40% male, 60% female	BCNU/CCNU 300 mg/m^2 etoposide 75-100 mg/m^2 cytosine arabinoside 75-100 mg/m^2 melphalan 50-100 mg/m^2 (n = 39).		
Burt et al. (2015)	Retrospective case series Median follow-up was 2 years (range 0.5 to 5 years) Single centre, USA.	N = 151, RRMS n = 123, SPMS n = 28 Inclusion criteria: 18-55 years, RRMS defined as acute relapses followed by partial or complete recovery and stable clinical manifestations between relapses, MS by McDonald criteria, EDSS 2 to 6, treatment unsuccessful by at least 1 FDA-approved drug and during the preceding year, had at least 2 relapses treated with corticosteroid or 1 relapse treated with a corticosteroid and additional Gd-lesions on MRI at a separate time. Median age: 37 years (range 18 to 60 years) Median MS duration: 5.1 years (range 0.75 to 22 years) Sex: 41.4% male; 58.6% females	Intermediate intensity conditioning: Cyc 50 mg/kg/day from day -5 to -2 (all patients) Either alemtuzumab 20 mg at day -2 (n = 22) or thymoglobulin 0.5 mg/kg at day 5, 1 mg/kg at day -4, 1.5 mg/kg from day -3 to -1 (n = 129)	• Disability as defined by EDSS where one point decrease was considered a significant improvement and one point increase was considered a significant progression. • Relapse-free survival • Safety • Progression-free survival Disease activity-free survival meaning no acute relapses, no progression and no Gd-enhanced or new lesions on MRI • NRS score • MSFC score • SF-36 score • New GAD-enhanced lesions on MRI • Total lesion volume on MRI	The conditioning treatments had by different patients was not defined.

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
Burman et al. (2014)	Retrospective case series, long-term observational follow-up Mean follow-up was 4 years (range 1 to 9 years). Multicentre (n = 7), Sweden	N = 48 for toxicity and AE outcomes (RRMS n = 40, SPMS n = 5, PPMS n = 2, PRMS n = 1), n = 41 for all analysed outcomes (RRMS n = 34) Inclusion criteria: not defined. Mean age at AHSCT: 31 years (range 9 to 52 years) Mean MS duration: 6.3 years (range 0.33 to 25 years); for RRMS 5.5 years (0.33 to 16 years) Sex: 46% male; 54% females	Intermediate intensity conditioning (BEAM, n = 41; Cyc-ATG, n = 7): BCNU 300 mg/m^2 cytosine arabinoside 800 mg/m^2 etoposide 800 mg/m^2 melphalan 140 mg/m^2 ATG 7.5-10 mg/kg (RRMS, n = 36; SPMS, n = 3; PPMS, n = 1; PRMS, n = 1) Cyc 200 mg/kg ATG 10 mg/kg (RRMS, n=4; SPMS, n=2; PPMS, n=1)	• Disease free survival at 5 years • Relapse free survival (no relapses) • MRI event free survival (no new MRI lesions) • Progression free survival (no EDSS progression) • Safety	
Mancardi et al. (2012)	Retrospective case series of EBMT registry patients, long-term observational follow-up. Median follow-up was 48.3 months (range 0.8 to 126 months) Multicentre (n = 17), Italy	N = 74 SPMS n = 41, RRMS n = 33 Shared criteria of registry cases: MS defined by Poser criteria with severe clinical course in last year defined as one point drop on EDSS despite conventional therapy. Mean age at AHSCT: 35.7 years (range 16 to 53 years) Mean MS duration: 11.2 years (range 1 to 28 years) Sex: NR	Intermediate intensity conditioning (BEAM-ATG): BCNU 300 mg/m^2 at day -6, cytosine arabinoside 200 mg/m^2 and etoposide 200 mg/m2 from day -5 to day -2, and melphalan 140 mg/m^2 at day -1. rATG added at total dose of 7.5-10 mg/kg at day +1 and +2	• Relapse (appearance of any new symptom or the recurrence of previously disappeared symptoms that lasted more than 24 hours without fever) Progression (an increase of 0.5 or 1 EDSS point at examination, if baseline was > 5.5 or ≤ 5.5 respectively, confirmed after 6 or 12 months) • Adverse events (early and late defined as within or after first 100 days post-AHSCT) • Neurological improvement post-AHSCT ○ If follow-up ≥ 12 months (n = 61), decrease of 0.5 or 1 EDSS point at examination, if baseline was > 5.5 or ≤ 5.5 respectively, confirmed after 6 or 12 months	

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
				○ If follow-up > 7 years (n = 18), EDSS used to categorise patients as either having sustained improvement, being stable or having progressed	
Krasulova et al. (2010)	Prospective case series, long-term follow-up. Median follow-up 66 months (range 11 to 132 months). Single centre, Czech Republic	N = 26 SPMS n = 15, RRMS n = 11 Inclusion criteria: MS defined by Poser criteria. Median age at AHSCT: 33 years (range 19 to 44 years) Mean MS duration: 7 years (range 2 to 19 years) Sex: 42% male, 58% female	Intermediate intensity conditioning (BEAM): BCNU 300 mg/m^2 at day -6, cytosine arabinoside 200 mg/m^2 and etoposide 200 mg/m2 from day -5 to day -2, and melphalan 140 mg/m^2 at day -1	• Relapse (occurrence of new MS symptoms or recurrence of previously recovered symptoms lasting at least 24 hours without fever) • Change in EDSS from baseline every 6 months post-AHSCT • Confirmed disability progression (defined as increase of 0.5 or 1 EDSS point at examination, if baseline was > 5 or ≤ 5 respectively, sustained for 6 months and measured at 6, 12 months and every year thereafter post-AHSCT) • PFS (measured by EDSS change and calculated by Kaplan-Meier method)	Patient numbers as presented based in Table 1 in the main report.
Applicable primary studies from Li et al. (2016), systematic review and meta-analysis					
Burt et al. (2009)	Prospective, single-arm phase I/II study Mean follow-up 37 months (range 24 to 48 months) Single centre, USA	N = 21 Inclusion criteria: MS by McDonald criteria, clinically definite MS by Poser criteria, 18-55 years, MS failed to respond to at least six months IFN-beta, EDSS 2.0-5.0 Median age at AHSCT: 33 years (range 20 to 53 years)	Intermediate intensity conditioning: Cyc 50 mg/kg/day from day -5 to -2 Either alemtuzumab 20 mg at day -2 (n = 17) or ATG 6 mg/kg/day over 5 days	• Progression free survival • Reversal of neurological disability (EDSS, NRS, 25-foot walk, nine-hole peg test: left hand, PASAT-2, PASAT-3)	

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
		Median MS duration pre-AHSCT: 5 years (range 1.5 to 10 years) Sex: male 48%, female 52%			
Applicable primary studies from SHTG Advice Statement 2019					
Muraro et al. (2017b)	Retrospective cohort study with long-term observational follow-up Median follow-up 6.6 years (range 0.2 to 16) Multicentre (n = 25), EBMT centres (mostly European) and CIBMTR (USA)	N = 281 RRMS n = 46, PRMS n = 17, PPMS n = 32, SPMS n = 186 Inclusion criteria: AHSCT for MS between 1995 and 2006, registered with either EBMT or CIBMTR Median age: 37 years (range 15 to 65) Median MS duration pre-AHSCT: 81 months (‹ 1 to 413) Sex: 41.6% male, 58.4% female	High intensity conditioning (18.9%): Cyc TBI ATG (n = 28) Busulfan Cyc ATG (n = 15) Busulfan ATG (n = 10) Intermediate intensity conditioning (63.7%): BEAM plus ATG (n = 109) BEAM (n = 40) Cyc plus thiotepa (n = 7) TLI plus melphalan (n = 5) Carmustine Cyc ATG (n = 18) Low intensity conditioning (17.4%): Cyc ATG (n = 46) Cyc fludarabine phosphate (n = 3)	• Progression free survival • Overall survival • Evolution of neurological disability (EDSS) • TRM • Late effects Association of demographic, MS disease related and treatment related information with outcomes	Very few RRMS patients relative to total patients and conditioning regimens very mixed (although mainly intermediate intensity).
Other primary studies					
Boffa et al. (2020)	Retrospective, case series. Mean follow-up was 50.9 months (± 48.2 months) for AHSCT and	N = 57 N = 25 AHSCT, N = 32 alemtuzumab Inclusion criteria: aggressive RRMS if one or more of the following were present: multiple (≥ 2) relapses with incomplete resolution in past year, > 2	Intermediate intensity conditioning (BEAM-ATG): BCNU 300 mg/m^2 at day -6, cytosine arabinoside 200 mg/m^2 and etoposide 200 mg/m^2 from day -5 to	• Time to relapse • Time to confirmed disability worsening • Time to evidence of MRI activity • Time to evidence of disease activity • ARR at 12, 24 and 36 months	This study was not randomised and patients in the AHSCT group had higher EDSS

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
	29.3 months (± 11.3 months) for alemtuzumab Single centre, Italy	MRI scans showing new or enlarging T2-lesions or Gd-lesions despite active treatment, EDSS ≥ 4 within 5 years of onset, no response to therapy with one or more DMTs for up to one year. Patients meeting Lorscheider criteria for SPMS were excluded. Mean (SD) age: 32.1 years (9.9 years) for AHSCT and 35.1 years (8 years) for alemtuzumab Mean (SD) disease duration: 9.5 years (5.4 years) for AHSCT and 7.2 years (5.9 years) for alemtuzumab Sex: 24% male; 76% female for AHSCT and 25% male, 75% female for alemtuzumab	day 2, and melphalan 140 mg/m^2 at day -1. rATG added at total dose of 3.75 mg/kg at day +1 and +2 after infusion	• EDSS	scores, ARRs and more advanced disease based on MRI than those in the alemtuzumab group.
Tappenden et al. (2019)	Matched-adjusted indirect comparison Mean follow up for AHSCT patients was 181 weeks (range 3 to 521 weeks). Median or mean duration of follow up was not reported for the natalizumab arm, but 92% of patients were followed up for at least 104 weeks. Multiple centres (number not clear)	Intervention arm: AHSCT. (n = 68) matched cohort of patients who received AHSCT, selected from four European registries. Baseline clinical characteristics which determined the need to undergo this treatment were based on European Group for Blood and Marrow Transplantation guidelines and recommendations, but without a study specific agreed standard, and criteria for implementing AHSCT were not a determinant of study inclusion. Control arm (n = 627): natalizumab. All patients included in the natalizumab arm of the AFFIRM trial, a randomised placebo-controlled trial. All patients had	Not reported	• EDSS disease progression (increase of ≥1 EDSS points; classified as 'sustained' disease progression if disease progression was present at two consecutive clinical assessments, irrespective of the interval between assessments)	Patients who received AHSCT were treated between 2004 and 2014. For patients treated with natalizumab, enrolment began in 2001; treatments dates/latest enrolment date is

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
		a diagnosis of RRMS. The AHSCT cohort were matched to the mean baseline characteristics of the natalizumab cohort using a logistic regression model which adjusted for covariates including disease duration (mean 5 years), number of relapses in the previous year (mean 1.53), and baseline EDSS score (mean 2.3).			unclear (the study results were published in 2006 (Polman et al. 2006)).
Dayama et al. (2020)	Observational cohort study, assumed to be retrospective Single centre, India Median follow-up duration was 242.5 days (range 110 to 380 days)	N = 20 RRMS n = 9, SPMS n = 11 Inclusion criteria: patients with MS (n = 20) who presented to the Hematology center of a tertiary care hospital in North India between January 2017 and January 2018 were included. Those with EDSS score <7 or who were less than 18 years old were excluded. Median age: 31.5 years (range 22–65 years) Mean (SD) MS duration at AHSCT: NR Sex: 35% male; 65% female	Rabbit anti-thymocyte globulin (ATG) [Sanofi] 0.5 mg/kg on day-6 and then 1 mg/kg on day-5 to day-2. Cyclophosphamide 50 mg/kg on day-5 to day-2 with mesna. Rituximab 375 mg/m^2 was given on day-7 and day +30 to prevent Epstein Barr virus reactivation secondary to ATG use.	• Change in EDSS score Progression free survival	One patient was lost to follow up after 110 days. Progression free survival is only reported for the whole cohort and not for the RRMS subgroup, and so is not reported here.
Kvistad et al. (2019)	Retrospective, observational case series Single centre, Norway Median follow-up was 26 months (11 to 48 months)	N = 30 Inclusion criteria: RRMS according to McDonald criteria, at least two clinical relapses the last year during immunomodulatory treatment, at least one Gd-lesion and/or new T2-lesions on MRI at two following MRI examinations the last year and a baseline EDSS score≤ 6. Relative criteria were disease	Intermediate conditioning: Cyc 50 mg/kg/day for 4 days with ATG, 0.5 mg/kg on day 1, 1 mg/kg on day -2 and 1.5 mg/kg over the following 3 days, given over 10 hours	• NEDA-3	

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
		duration less than six years and an age ≤ 45 years. Median age at AHSCT: 29.5 years (range 15 to 44 years) Median disease duration pre-AHSCT: 5 years (range 2 to 10 years)			
Bose et al. (2019)	Single-arm, phase II trial. Strict 36 months follow-up Multicentre (n = 3), Canada clinicaltrials.gov: NCT01099930	N = 23 RRMS n = 12, SPMS n = 11 Inclusion criteria taken from Atkins et al. (2016): 18-50 years, multiple early relapses, early development of sustained disability (EDSS) specifically affecting motor control with cerebellar or pyramidal KFS scores of at least 3 within 5 years of disease onset, evidence of ongoing clinical disease activity despite at least one year of immune-modulatory/-suppressive treatment, EDSS of 3-6 with a cerebellar or pyramidal KFS of at least 3, and MRI satisfying Paty or Fazekas criteria. Mean age: 33 years (range 24 to 45 years) Mean (SD) MS duration at AHSCT: NR Sex: 39% male; 61% female	High intensity conditioning: Busulfan with monitoring of first dose pharmacokinetics, administered every 6 h for 16 doses from day -10 to -6, Cyc (50 mg/kg per day, intravenously) from day -5 to -2, and rATG (1· 25 mg/kg per day, intravenously) from day -4 to -1.	• Change in mFIS • Change in FIS subcategories (cognitive, physical, social) • Change in global FIS	This study is an extension to the Atkins et al. (2016) publication.
Moore et al. (2019)	Prospective, single-arm, phase II trial Median follow-up 36 months (range 12 to 66 months)	N = 35 RRMS n = 20, SPMS n = 15 Inclusion criteria: MS by McDonald criteria, 18-60 years, trialled ≥ 2 DMTs, EDSS 2.0-7.0	Intermediate intensity conditioning (BEAM): BCNU 300 mg/m^2 at day -6, cytosine arabinoside 200 mg/m^2 and etoposide 200 mg/m^2 from day -5 to	• Event free survival (authors related this to NEDA outcome) • EDSS • MRI related changes • Restart of DMT • Changes in MS QoL	

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
	Single centre, Australia anzctr.org.au number: ACTRN12613000339752	Median age at AHSCT: 37 years (range 21 to 55) Median MS duration pre-AHSCT: 83 months (range 8 to 259) Sex: 31% male, 69% female	day -2, and melphalan 140 mg/m^2 at day -1.	• Immunological reconstitution profiles post-AHSCT	
Ruiz-Arguelles et al. (2019)	Feasibility study Median follow-up was 12 months (3 to 42 months) Single centre, Mexico clinicaltrials.gov: NCT02674217	N = 617 RRMS n = 259, SPMS n = 228, PPMS n = 130 Inclusion criteria: RRMS, SPMS, PPMS considered suitable if, two weeks prior to AHSCT, Karnofsky performance status › 70% and EDSS ≤ 8 Median age: 46 years (range 18 to 73 years) Mean (SD) MS duration at AHSCT: NR Sex: 35%% male; 65% female	Intermediate intensity conditioning: “ Mexican method” Mobilisation by Cyc (50 mg/kg) on days -11 and -10 and G-CSF (10 microgram/kg/bid) on days -9 to -1. Apheresis was performed on day -2. Cyc (50 mg/kg) over 120 min on days -2 and -1 followed by mesna (1000 mg/m^2), ondansetron (8 mg), dexamethasone (4 mg) and pantoprazole (40 mg). After Cyc, ondansetron (4 mg every 12 h after chemo), oral cotrimoxazole (800/160 mg every 24 h), oral fluconazole (200 mg) and oral acyclovir (400 mg every 12 h) administered until granulocytes increased above 0.5 x 10^9/L. Post-AHSCT and once granulocytes had recovered, rituximab (375 mg/m^2) over three hours, followed by	• Recovery of granulocyte and platelet counts • TRM • Overall survival Clinical response (self-reported EDSS)	AHSCT performed on outpatient basis (32 individuals required hospitalisation). Patients were instructed to provide information on their neurological status and adverse events every three months post AHSCT.

Study	Study design plus identifier number	Participants	Conditioning regimen	All outcomes	Comments
			rituximab (100 mg) every two months for one year (n = 63). Subsequent patients received rituximab (1000 mg) after granulocyte recovery.		
Mehra et al. (2019)	Retrospective case series. Median follow-up was 436 days (188 to 785 days) Single centre, London	N = 36 RRMS n = 22, SPMS n = 10, PPMS n = 4 Inclusion criteria: NR Mean age at AHSCT: 43.5 years (range 36 to 47 years) Median MS duration at AHSCT: NR Sex: 52.8% male, 47.2% female	Intermediate intensity conditioning: BEAM-rATG conditioning (n = 1) NS Cyc-ATG conditioning (n = 35) Cyc (50 mg/kg per day) for 4 days and rATG (2.5 mg/kg per day) for 3 days	• EBV reactivation biomarkers • Lymphoproliferative disorder	
Comini-Frota et al. (2019)	Prospective comparative case series with long term follow up. Follow-up: NR Multicentre (n = 2), Brazil	N = 10, RRMS N = 5 received AHSCT, N = 5 did not due to expense Inclusion criteria: NR Age at AHSCT: NR MS duration: NR Sex: 20% male, 80% female	Intermediate intensity conditioning: Cyc-ATG conditioning, NS	• EDSS • MRI • Clinical examination • NEDA	Poorly reported, outcomes not stated prior. Related study by de Rodrigues et al. (2013) used to source information for table.

AHSCT: autologous haematopoietic stem cell transplant; ARR: annualised relapse rate; ATG: anti-thymocyte globulin; BEAM: BCNU, etoposide, cytosine-arabinoside, melphalan; BCNU: bis-chloroethylnitrosourea (carmustine); CCNU: lomustine; CIBMTR: Center for International Blood and Marrow Transplant Research; Cyc-ATG: cyclophosphamide-antithymocyte globulin; DMT: disease modifying therapy; EBMT: European Society for Blood and Marrow Transplantation; EBV: epstein-barr virus; EDSS: expanded disability status scale; FDA: Federal Drug Administration; G-CSF: granulocyte colony-stimulating factor; Gd: gadolinium; IFN: interferon; iGg: immunoglobulin G; KFS: kaplan-feinstein scale; mFIS: modified fatigue impact scale;. MRI: magnetic resonance imaging; MS: multiple sclerosis; MSIS 29: MS Impact Scale; MSFC: MS functional composite; MSIS-29: multiple sclerosis impact scale; NEDA: no evidence of disease activity; NR: not reported; NRS: numeric rating scale; NS: not specified; PASAT: paced auditory serial addition test; PFS: progression free survival; PPMS: primary progressive MS; PRMS: progressive relapsing MS; rATG: rabbit anti-thymocyte globulin RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; SF-36: 36-item short form survey; SPMS: secondary progressive multiple sclerosis; SHTG: Scottish Health Technologies Group; SRD: sustained recovery in disability; TBI: total body irradiation; TLI: total lymphoid irradiation

Appendix 4. Table 8: AHSCT clinical outcomes

Study	RRMS participants (of total)	Outcome	Comments
Relapse, annualised relapse rate			
Boffa et al. (2020)	N = 25 AHSCT N = 32 alemtuzumab	AHSCT group: decrease from 3.2 (± 1.7) at baseline to 0.0, 0.1 and 0.05 at one-, two- and three-years post AHSCT. Alemtuzumab group: decrease from 1.7 (± 1.6) at baseline to 0.17, 0.9 and 0.35 at one-, two- and three-years post AHSCT. ARR at one- and three-years post-AHSCT was significantly lower in AHSCT compared with alemtuzumab (p = 0.03 and p = 0.02 respectively). ARR did not differ between groups at two-years post-AHSCT.	At baseline, the AHSCT group had higher ARR than the alemtuzumab group (p = 0.001)
Casanova et al. (2017)	N = 28 (38)	Decrease from 1.6 one-year pre-AHSCT to 0.0 in first year post-AHSCT, increased to 0.22 from years two to five post-AHSCT and decreased to 0.05 from years six to seven	Statistical analysis not provided
Burman et al. (2014)	N = 34 (41)	Decrease from 4.1 (range 0-12) one-year pre-AHSCT to 0.03 post-AHSCT ARR for RRMS patients only was 4.8 (range 0-12) one-year pre-AHSCT (post-AHSCT ARR for RRMS patients only NR)	Statistical analysis not provided
Krasulova et al. (2010)	N = 11 (26)	Decrease from 2 one-year pre-AHSCT to 0 in first two years post-AHSCT (p = 0.045)	
Relapse free survival			
Boffa et al. (2020)	N = 25 AHSCT N = 32 alemtuzumab	AHSCT group: 84% at end of observation period Alemtuzumab group: 69% at end of observation period AHSCT significantly reduced relapse free survival compared with alemtuzumab (HR 0.13, 95% CI: 0.02 to 0.63; p = 0.012)	
Comini-Frota et al. (2019)	N = 5 (5)	100% at five-years post-AHSCT	Statistical analysis not provided, not feasible with small study number
Moore et al. (2019)	N = 20 (35)	97% (95% CI: 81 to 100) at one year and 90% (95% CI: 73 to 97) at two- and three-years post-AHSCT	
Nash et al. (2017)	N = 24 (24)	86.9% (90% CI: 69.5 to 94.7) at five years post-AHSCT	

Study	RRMS participants (of total)	Outcome	Comments
Burt et al. (2015)	N = 123 (151)	89% (95% CI: 81 to 94) at two years post-AHSCT 80% (95% CI: 69 to 88) at four years post-AHSCT	
Burman et al. (2014)	N = 34 (41)	87% at five years post-AHSCT	Statistical analysis not provided
Mancardi et al. (2012)	N = 33 (74)	85% at five years post-AHSCT (n = 61; RRMS, n = 26) Relapse rate higher for RRMS patients (30%) than SPMS patients (10%, p = 0.03)	
Burt et al. (2009)	N = 21 (21)	76% after mean of 37 months (range 24 to 48)	
Relapses			
Kvistad et al. (2019)	N = 30	10% of patients had relapses post-AHSCT	
Burt et al. (2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	2% of patients in AHSCT group relapsed after one year compared with 69% in DMT group (between group difference 78%; 95% CI: 64 to 88; p < 0.001)	
Frau et al. (2018)	N = 5 (9)	Comparing relapse frequency two years pre-AHSCT and two years post-AHSCT, the frequency was significantly reduced (p = 0.041). All patients experienced either relapse or disability progression (range 7 to 118 months).	
Disease progression			
Burt et al. (2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	AHSCT group: 1.92% (95% CI: 0.27 to 12.9) at one- and two-years post-AHSCT, 5.19% (95% CI: 1.26 to 20.1) at three years post-AHSCT and 9.71% (95% CI: 3.0 to 28.8) at four- and five-years post-AHSCT. DMT group: 24.5% (95% CI: 14.7 to 39.1) at one year post-AHSCT, 54.5% (95% CI: 40.7 to 69.4) at two years post-AHSCT, 62.5% (95% CI: 48.3 to 76.7) at three years post-AHSCT, 71.2% (95% CI: 56.8 to 84.2) at four years post-AHSCT and 75.3% (95% CI: 60.4 to 87.8) at five years post-AHSCT.	

Study	RRMS participants (of total)	Outcome	Comments
Tappenden et al. (2019)	N = 68	HR for sustained EDSS progression, AHSCT versus natalizumab: 0.11 (95% CI 0.02, 0.76)	Unsustained EDSS progression was also investigated, but the Kaplan-Meier progression-free survival functions for the two treatment groups crossed. Authors therefore did not report HR for this outcome.
Progression free survival			
Dayama et al. (2020)	N=9 (20)	100% at one-year post-AHSCT	
Moore et al. (2019)	N = 20 (35)	85% (95% CI: 68% to 94%) at one year, 78% (95% CI: 59% to 89%) at two years and 73% (95% CI: 53% to 86%) at three years post-AHSCT For RRMS patients, 95% (95% CI: 72% to 99%) at one year, 88% (95% CI: 60% to 97%) at two- and three-years post-AHSCT, this was statistically significantly higher than rates for SPMS patients (p = 0.04).	
Muraro et al. (2017b)	N = 46 (281)	46% (95% CI: 42 to 54) at five years post-AHSCT For RRMS, 73% (95% CI: 57 to 88) at five years post-AHSCT	
Nash et al. (2017)	N = 24 (24)	69.2% (90% CI: 50.2 to 82.1) at five years post AHSCT	This endpoint was considered comparable, not identical, to NEDA
Burt et al. (2015)	N = 123 (151)	92% (95% CI: 85% to 96%) at two years post-AHSCT 87% (95% CI: 78% to 93%) at four years post-AHSCT	
Burman et al. (2014)	N = 34 (41)	77% at five years post-ASHCT	Statistical analysis not provided

Study	RRMS participants (of total)	Outcome	Comments
Mancardi et al. (2012)	N = 33 (74)	66% (SE = 7%) at five years post-AHSCT	After a median follow-up period of 48.3 months (range = 0.8–126), 19 out of 74 treated cases had progressed and PFS at 5 years was 66% (SE = 7%)
Krasulova et al. (2010)	N = 11 (26)	70.8% at three years post-AHSCT 29.2% at six years post-AHSCT 84.4% at three years post-AHSCT in RRMS patients (n = 11) compared with 60% in SPMS patients (n = 15); difference in PFS curves *F*(2,26) = 16.65527, p = 0.00002	CI not reported due to low data availability
Burt et al. (2009)	N = 21 (21)	100% at mean of three years post AHSCT	
Disease free progression (including event/activity/disease)			
Nash et al. (2017)	N = 24 (24)	69.2% (90% CI: 50.2% to 82.1%) at five years post-AHSCT	
Atkins et al. (2016)	N = 12 (24)	69.6% (95% CI: 46.6% to 84.2%) at three years post-AHSCT	
Shevchenko et al. (2015)	N = 43 (99)	80% (95% CI: 67.6% to 88.1%) at median follow-up of 48.9 months post-AHSCT 83.3% (95% CI: 59.4% to 93.8%) in RRMS patients compared with 75.5% (95% CI: 58% to 86.5%) in progressive types of MS (p > 0.05)	36 months (range 6 to 60.9 months) median time to disease progression; this was 58 months (range 42 to 60.9 months) in
Burt et al. (2015)	N = 123 (151)	80% (95% CI: 70% to 86%) at two years post-AHSCT 68% (95% CI: 56% to 77%) at four years post-AHSCT	RRMS compared with 24 months (range 6 to 42 months) in PRMS
Burman et al. (2014)	N = 34 (41)	68% at five years post-AHSCT	Statistical analysis not provided

Study	RRMS participants (of total)	Outcome	Comments
No evidence of disease activity			
Boffa et al. (2020)	N = 25 AHSCT N = 32 alemtuzumab	AHSCT group: NEDA-3 was reached by 75% at end of observation period Alemtuzumab group: NEDA-3 was reached by 56% at end of observation period AHSCT significantly reduced NEDA-3 compared with alemtuzumab (HR 0.27, 95% CI: 0.08 to 0.84; p = 0.023)	
Tolf et al. (2019)	N = 10	NEDA-4 was reached by 50% while NEDA-3 was reached by 70%.	The timeframe for NEDA is at least five years post-AHSCT. NEDA-4 considered similar to sustained complete remission whereby the following criteria are fulfilled for at least a 5-year period: no clinical relapse, no EDSS progression, no MRI event, no ongoing atrophy and no DMTs started. NEDA-3 defined as no clinical relapse, no EDSS progression and no MRI event (no timeframe defined)
Kvistad et al. (2019)	N = 30	At 24 months post-AHSCT, NEDA-3 was reached by 76% (n = 13 of 17)	NEDA-3 defined as composite score comprising absence of clinical relapses and sustained disability progression in addition to no new MRI disease activity on MRI examinations for the given period (no timeframe defined)

Study	RRMS participants (of total)	Outcome	Comments
Burt et al. (2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	AHSCT group: 98.1% (95% CI: 87.4% to 99.7%) at six months and one year post-AHSCT, 93.3% (95% CI: 80.6% to 97.8%) at two years post-AHSCT, 90.3% (95% CI: 75.9% to 96.3%) at three years post-AHSCT and 78.5% (95% CI: 59.8% to 89.5%) at four- and five-years post-AHSCT DMT group: 39.6% (95% CI: 26.6% to 52.39%) at six months post-AHSCT, 20.8% (95% CI: 11% to 32.5%) at one year post-AHSCT, 11.9% (95% CI: 4.3 to 23.6) at two years post-AHSCT, 5.93% (95% CI: 1.17% to 16.6%) at three years post-AHSCT, 2.97% (95% CI: 0.24% to 12.8%) at four- and five-years post-AHSCT	NEDA defined as no progression, relapses, new or enlarging lesions (no timeframe defined)
Moore et al. (2019)	N = 20 (35)	82% (n = 34, 95% CI: 65 to 92) at one year, 65% (n = 20, 95% CI: 45% to 79%) at two years and 60% (n = 14, 95% CI: 40% to 75%) at three years post AHSCT For RRMS patients, 90% (n = 20, 95% CI: 66% to 97%) at one year, 70% (n = 11, 95% CI: 41% to 87%) at two and three years (n = 8) post AHSCT	An absence of any of the following: relapse, new/ enlarging T2 lesions and/or new gadolinium enhancing lesions on MRI following baseline MRI scan at 6 months or sustained EDSS progression measured and consistent with NEDA-3 terminology
Comini-Frota et al. (2019)	N = 5 (5)	NEDA ranged between five years (n = 1) and nine years (n = 2) post-AHSCT	NEDA at five years post-AHSCT not defined
Casanova et al. (2017)	N = 28 (38)	27.3% RRMS patients (n = 6 of 22) experienced relapse while 88.9% SPMS patients (n = 8 of 9) experienced either relapse or progression, this difference was statistically significant (p = 0.004)	NEDA defined as absence of relapses and/or increases of disability according to previous definition and no new T2 lesions or Gd-enhanced lesions in MRI performed at last control

Study	RRMS participants (of total)	Outcome	Comments
Neurologic Rating Scale			
Burt et al. (2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	Increase from mean 79.5 (SD 10.2) at baseline to 88.3 (SD 9.15) at one-year post-AHSCT for AHSCT group (n = 50 at one-year) compared with decrease from 81.1 (SD 10.9) at baseline to 79.5 (SD 11.8) after one-year of trial for DMT (n = 48 at one-year). Between group difference in means 9.8 (95% CI: 6.26 to 14.72; p ‹ 0.001). Between group difference in means from baseline to one-year 11.2 (95% CI: 8.08 to 14.29; p = 0.001)	
Burt et al. (2009)	N = 21 (21)	Increase by ≥ 10 (n = 14) and by ‹ 10 (n = 5) at last follow-up compared with baseline (p = 0.0001)	NR for n = 2
Expanded disability status scale (EDSS)			
Boffa et al. (2020)	N = 25 AHSCT N = 32 alemtuzumab	AHSCT group: Improvement at one-year post-AHSCT (p < 0.001) Alemtuzumab group: Improvement at one-year post-AHSCT (p = 0.001) AHSCT significantly improved EDSS compared with alemtuzumab (p = 0.035)	At baseline, the AHSCT group had higher EDSS than the alemtuzumab group (p < 0.001)
Tolf et al. (2019)	N = 10 (10)	Median improvement of 3 (range 0.5 to 7.5) by the end of the study. Decrease of median 6.5 (range 2.5 to 8) pre-AHSCT to 1.75 (range 0 to 6) at the end of the study.	
Kvistad et al. (2019)	N = 30 (30)	43% of patients (n = 13) had sustained improvement in EDSS compared to pre-AHSCT EDSS with median decrease of 1 and maximal decrease of 5. 50% of patients (n = 15) had stabilisation of EDSS post-AHSCT and 7% of patients (n = 2) had a progression of EDSS post-AHSCT.	
Bose et al. (2019)	N = 12 (23)	Increase from 5 (range 4 to 6) at baseline to 5.5 (range 3.6 to 6.5) at trial's end, p = 0.78	
Burt et al. (2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	Decrease from mean 3.4 (SD 1.2) at baseline to 2.4 (1.4) at one-year post-AHSCT for AHSCT group (n = 50 at one-year) compared with increase from 3.3 (1) at baseline to 4 (1.7) after one-year of trial for DMT (n = 48 at one-year). Between group difference in means -1.62 (95% CI: -2.24 to -0.99; p ‹ 0.001). Between group difference in means from baseline to one-year -1.7 (95% CI: -2.03 to -1.29; p ‹ 0.001)	
Moore et al. (2019)	N = 20 (35)	Decrease (mean) of 1.325 (p = 0.0008) at one year, 1.208 (p = 0.0037) at two years and 1.484 (p = 0.0088) at three years post-AHSCT	
Comini-Frota et al. (2019)	N = 5 (5)	No summary data reported	

Study	RRMS participants (of total)	Outcome	Comments
Frau et al. (2018)	N = 5 (9)	Comparing EDSS pre-AHSCT and one-year post-AHSCT, no significant difference was found (p = 0.4)	
Muraro et al. (2017b)	N = 46 (281)	Decrease (mean) of 0.32 (95% CI: 0.15 to 0.49) at one-year post-AHSCT (p ‹ 0.001) For RRMS patients (n = 32), -0.76 (95% CI: -1.08 to +0.34) at one-year post-AHSCT compared with -0.14 (95% CI: -0.28 to +0.01) at the same time for progressive MS types (n = 79)	
Casanova et al. (2017)	N = 28 (38)	Decrease (mean) from 5 (SD, 1.3) at baseline to 3.4 (SD, 1.2) for RRMS patients at minimum two years post-AHSCT (n = 22) Increase (mean) from 6.1 (SD, 0.6) at baseline to 7.2 (SD, 1.7) for SPMS patients at minimum two years post-AHSCT (n = 9)	
Nash et al. (2017)	N = 24 (24)	Decrease (median) of 0.5 (range -1.5 to 0) from baseline at five years post-AHSCT (p = 0.001)	
Atkins et al. (2016)	N = 12 (24)	40% cumulative incidence of improvement in EDSS at 7.5 years post-AHSCT	Post-hoc analysis: EDSS stabilised or improved in 91% (n = 11) with baseline MSSS ≤ 8.3. EDSS progressed in 50% (n = 12) with baseline MSSS › 8.3.
Shevchenko et al. (2015)	N = 43 (99)	Decrease (median) of ≥ 0.5 from baseline at 62 months (median follow-up) for 47% of patients post-AHSCT	
Burt et al. (2015)	N = 123 (151)	Decrease from 4 at baseline to 3 at 6 months, 1 year and 2 years post-AHSCT and to 2.5 at 3-, 4- and 5-years post-AHSCT (p ‹ 0.001 at all intervals except 5 years when p = 0.009)	
Burman et al. (2014)	N = 34 (41)	Decrease from 5.5 (range 1.5 to 8.5) at AHSCT to 3.25 (range 0 to 7) at one-year post-AHSCT and to 3 (range 0 to 7) at two-years post-AHSCT for RRMS patients	Median change -0.75 (range -7 to 1.5); -1.5 (range -7 through 1.5) if progressive patients excluded. Greatest EDSS improvement was within first year post-AHSCT.

Study	RRMS participants (of total)	Outcome	Comments
Mancardi et al. (2012)	N = 33 (74)	Decrease of >1 for 31% of RRMS patients, of 0.5 to 1 for 23% of RRMS patients and no change for 46% of RRMS patients at one-year post-AHSCT. Decrease of >1 for 3% of SPMS patients, of 0.5 to 1 for 37% of SPMS patients and no change for 60% of SPMS patients one-year post-AHSCT (p = 0.009).	
Burt et al. (2009)	N = 21 (21)	Decrease ≥ 1 for 81% of patients compared with baseline, 0.5 for 9.5% and no change for 9.5%	Improvement for all patients compared with baseline statistically significant (p ‹ 0.0001)
Dayama et al. (2020)	N = 9 (20)	Improvement in EDSS reported in 6/9 patients with RRMS	
Patient reported EDSS			
Ruiz-Arguelles et al. (2019)	N = 259 (617)	At one-year post-AHSCT, 47% reported improvement in EDSS and 31% reported stabilisation in EDSS. EDSS was assessed 3, 6, 9, 12, and 15 months post-AHSCT and was found to decrease from a mean of 5.1 to a mean of 4.5 (p = 0.0002). EDSS response rate (improvement plus stabilisation) was 83% in RRMS patients, 78% in PPMS patients and 73% in SPMS patients.	Compliance was 240 patients at one-year, 136 at two-years and 19 at three-years post-AHSCT.
Death/treatment related mortality			
Dayama et al. (2020)	N = 9 (20)	No death/TRM	
Boffa et al. (2020)	N = 25 AHSCT N = 32 alemtuzumab	No death/TRM	
Tolf et al. (2019)	N = 10	No death/TRM	
Kvistad et al. (2019)	N = 30	No death/TRM	

Study	RRMS participants (of total)	Outcome	Comments
Burt et al. (2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	No death/TRM	
Moore et al. (2019)	N = 20 (35)	No death/TRM	
Frau et al. (2018)	N = 5 (9)	No death/TRM	
Muraro et al. (2017b)	N = 46 (281)	37 deaths during entire follow-up (median follow up 6.6 years (range 0.2 to 16))/eight TRM (2.8%; 95% CI: 1% to 4.9%) within 100 days of AHSCT	TRM: two patients died from infection, one died from an accident, one died from veno-occlusive disease, one from haemorrhage, one from EBV lymphoproliferative disorder and two died from unreported causes. Among the patients who died during follow-up, progressive forms of MS and high-intensity conditioning were over-represented compared with the frequency of these factors in the entire cohort (although the small number precludes a formal statistical evaluation).
Bose et al. (2019)	N = 12 (23)	NR	
Ruiz-Arguelles et al. (2019)	N = 259 (617)	No death over 30-months/TRM over 30-months	
Mehra et al. (2019)	N = 22 (36)	NR	
Comini-Frota et al. (2019)	N = 5 (5)	No death/TRM	

Study	RRMS participants (of total)	Outcome	Comments
Casanova et al. (2017)	N = 28 (38)	No death/TRM	
Nash et al. (2017)	N = 24 (24)	No death/TRM	
Atkins et al. (2016)	N = 12 (24)	One TRM	TRM: massive hepatic necrosis following sinusoid obstruction syndrome and *Klebsiella* sepsis 62 days after transplantation
Shevchenko et al. (2015)	N = 43 (99)	No death/TRM	
Burt et al. (2015)	N = 123 (151)	No death/TRM	
Burman et al. (2014)	N = 34 (41)	No death/TRM	
Mancardi et al. (2012)	N = 33 (74)	Three deaths/two TRM	TRM: one patient had engraftment failure and died 24 days post-AHSCT due to an opportunistic infection caused by *Actinomyces species* and disseminated intravascular coagulation; the second patient had encephalopathy, not due to infection, and died one month post-AHSCT
Krasulova et al. (2010)	N = 11 (26)	Two deaths/no TRM	
Burt et al. (2009)	N = 21 (21)	No death/TRM	

Study	RRMS participants (of total)	Outcome	Comments
Overall survival			
Burt et al. (2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	NR	
Ruiz-Arguelles et al. (2019)	N = 259 (617)	100% at 30 months post-AHSCT	
Muraro et al. (2017b)	N = 46 (281)	93% (95% CI: 89% to 96%) at five years post-AHSCT	
Nash et al. (2017)	N = 24 (24)	86.3% (90% CI 68.3%–94.5%) at median follow-up 62 months (range 12 to 72 months)	
Atkins et al. (2016)	N = 12 (24)	95% beyond 62 days post-AHSCT	
Fatigue			
Bose et al. (2019)	N = 12 (23)	Decrease (median) in modified fatigue impact scale from 36 (range 30 to 46.5) at baseline to 23 (range 9 to 41.5) at 36 months (p = 0.001)	
MRI related changes			
Kvistad et al. (2019)	N = 30	New lesions in three patients post-AHSCT	Two of the three patients had experienced clinical relapse
Comini-Frota et al. (2019)	N = 5 (5)	No new lesions after five years	
Frau et al. (2018)	N = 5 (9)	New lesions in six patients post-AHSCT (range 11 to 120 months) and new Gd-lesions in seven patients post-AHSCT (range 8 to 120 months)	
Nash et al. (2017)	N = 24 (24)	New lesions in two patients at 45.6- and 48.4-months post-AHSCT	
Atkins et al. (2016)	N = 12 (24)	No new lesions, 0% of patients (95% CI: 0% to 14.8%) and 327 MRI scans, up to 13 years post-AHSCT (range 3.9 to 12.7)	
Burt et al. (2015)	N = 123 (151)	Decrease in mean number of Gd-lesions from 3.22 at 3 to 6 months pre-AHSCT to 2.57 at 3 months, 0.01 at 6 months, 0.13 at 1 year, 0.07 at 2 years, 0.24 at 3 years, 0.67 at 4 years and 0.08 at 5 years post-AHSCT (p ‹ 0.001).	

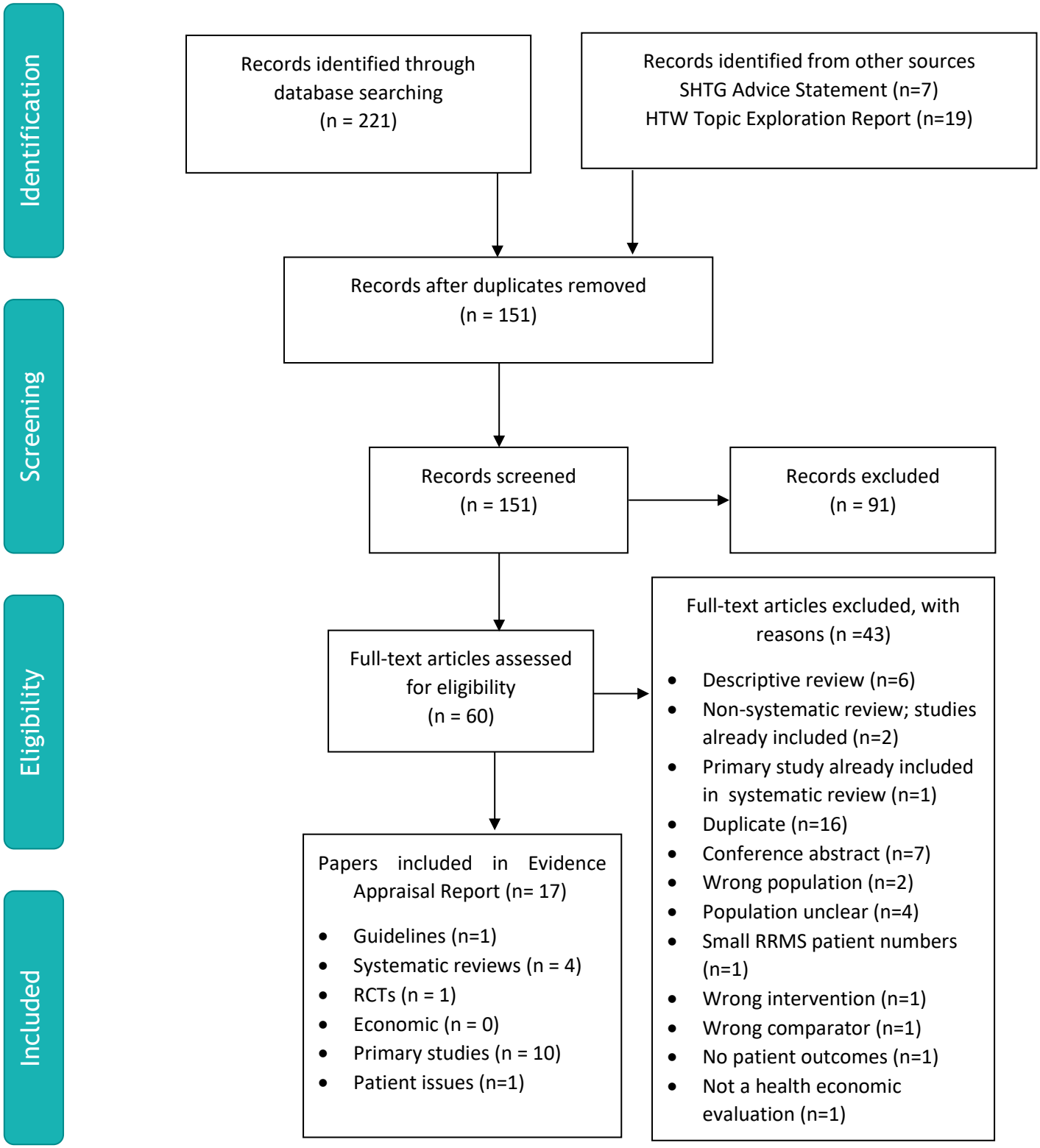
Study	RRMS participants (of total)	Outcome	Comments
MRI activity free survival			
Boffa et al. (2020)	N = 25 AHSCT N = 32 alemtuzumab	AHSCT group: 85% at end of observation period Alemtuzumab group: 59% at end of observation period AHSCT significantly improved MRI activity free survival compared with alemtuzumab (HR 0.13, 95% CI: 0.03 to 0.59; p = 0.009)	
Nash et al. (2017)	N = 24 (24)	86.3% (90% CI: 68.1% to 94.5%) at five years post-AHSCT	
Burman et al. (2014)	N = 34 (41)	85% at five years post-AHSCT	
MRI T-2 weighted lesion volume			
Burt et al. (2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	Decrease from 100% at baseline to 68.3% (SD 20.7) at one-year post-AHSCT for AHSCT group (n = 48 at one-year) compared with increase from 100% at baseline to 134.3% (45.6) after one-year of trial for DMT (n = 49 at one-year). Between group difference in means -66.19 (95% CI: -75.17 to -57.21; p ‹ 0.001). Between group difference in means from baseline to one-year -66 (95% CI: -70.6 to -61.3; p ‹ 0.001)	
Burt et al. (2015)	N = 123 (151)	Decrease of 33% from median 8.57 cm^3 (range 2.78 to 22.08, mean (SD) 15.69 cm3 (18.09), 95% CI: 12.53 to 18.54) pre-AHSCT to a median of 5.74 cm^3 (range 1.88 to 14.45, mean (SD) 10.92 cm3 (12.60), 95% CI: 8.72 to 13.12) post-AHSCT, p ‹ 0.001 (n = 128)	
EBV biomarkers			
Mehra et al. (2019)	N = 22 (36)	Median time 30 days (range 23 to 46) to first EBV DNA detection post-AHSCT Median time 32 days (range 31 to 53) to peak EBV DNA levels post-AHSCT	27.6% (n = 8) developed symptomatic EBV reactivation. Three patients had findings consistent with probable lymphoproliferative disorder.
MS functional composite score			
Burt et al. (2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	Mean increase of 0.32 at one-year post-AHSCT for AHSCT group and decrease of 0.31 at one-year post-AHSCT for DMT group. Between group difference in changes from baseline: 0.51 (95% CI: 0.28 to 0.72; p < 0.001)	

Study	RRMS participants (of total)	Outcome	Comments
Nash et al. (2017)	N = 24 (24)	The score has statistically significantly improved from baseline at one-year post-AHSCT (p = 0.032) and continued for two- (p = 0.013) and three-years (p = 0.011) post-AHSCT. There was no statistically significant difference from baseline at four-years post-AHSCT	
Burt et al. (2015)	N = 123 (151)	Median scores were 0.38 (range -0.01 to 0.64) at two-years post-AHSCT (p < 0.001) and 0.45 (range 0.04 to 0.6) at four-years post-AHSCT (p = 0.02)	
9-hole peg test			
Burt et al. (2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	In AHSCT arm, decrease (mean) from 30.81 seconds at baseline to 26 seconds at six-months post-AHSCT . At one year post-ASCT, 24 seconds for AHSCT group. In DMT arm, increase from 24.69 seconds at baseline to 26.28 seconds at six-months post-AHSCT and to 25.64 seconds at one-year post-AHSCT for DMT group Between group difference in change in scores at one-year post-AHSCT was -8.03 (95% CI: -11.3 to -4.76; p < 0.001)	Crossover permitted in MIST trial for DMT arm after year 1.
Burt et al. (2009)	N=15 (nine-hole peg test, left hand)	Scores on the right-hand nine-hole peg test and the left-hand nine-hole peg test improved but did not change significant from baseline (p=0.10 and p=0.12).	
Nash et al. (2017)	N = 24 (24)	No significant change from baseline in nine-hole peg test results over five years of follow-up	Study reports MSFC (composite) and MSFC components, which include 'MSFC nine-hole peg test'
Paced Auditory Serial Addition Test			
Burt et al. (2019)	N = 52 (52) AHSCT group N = 51 (51) DMT group	The mean PASAT scores improved in both the AHSCT and DMT arms, with no statistically significant difference between groups at year 1. Difference 0.22% (95% CI -72.4% to 72.9%).	
Nash et al. (2017)	N = 24 (24)	Score statistically significantly improved from baseline at one-year post-AHSCT (p < 0.001) and continued for two- (p = 0.016) and three-years (p = 0.016) post-AHSCT. No statistically significant difference at four-years post-AHSCT.	Study reports MSFC (composite) and MSFC components, including 'MSFC PASAT-3'

Study	RRMS participants (of total)	Outcome	Comments
Burt et al. (2009)	N=15/16 (PASAT-2/PASAT-3, 6 months post-transplant)	Scores on the 2-second and 3-second PASAT improved after transplantation (p=0.009 and p=0.014)	

AHSCT: autologous haematopoietic stem cell transplant; ARR: annualised relapse rate; DMT: disease modifying therapy EBV: epstein-barr virus; EDSS: expanded disability status scale; Gd: gadolinium; HR: hazard ratio. MRI: magnetic resonance imaging; MS: multiple sclerosis; MSIS 29: MS Impact Scale; MSFC: MS functional composite; MSIS-29: multiple sclerosis impact scale; NEDA: no evidence of disease activity; NR: not reported; PFS: progression free survival; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; SPMS: secondary progressive multiple sclerosis; TRM: transplant-related mortality

Appendix 5. PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness (from April 2019 – June 2020)



Appendix 6. Original cost effectiveness analysis

1. Introduction

The review of the clinical effectiveness evidence for this question, based on an update of the search originally undertaken by SHTG, found no additional RCTs published since the SHTG advice statement (SHTG 2019). While further observational studies were identified and included in the evidence review, the MIST RCT represents the highest level of clinical evidence available (Burt et al. 2019).

In the MIST RCT, people with RRMS who experienced at least two relapses while receiving DMT in the prior year, and with an EDSS score of 2.0 to 6.0 were randomised between the intervention: AHSCT along with cyclophosphamide (200mg/kg) and antithymocyte globulin (6mg/kg) and the comparator: switching to a DMT of higher efficacy or a different class than DMT taken during the previous year (Burt et al. 2019).

SHTG demonstrated in their advice statement that the applicability of the MIST RCT to NHS Scotland may be limited, due to the exclusion of certain high-efficacy DMTs (SHTG 2019). These include ocrelizumab and alemtuzumab. Ocrelizumab was excluded as patient recruitment for the trial was completed prior to the FDA approval of the drug. Alemtuzumab was excluded due to the risk of drug-related persistent lymphopenia and autoimmune disorders which might increase the risk of AHSCT in people who crossover to the AHSCT arm, which was permitted after one year (Burt et al. 2019).

SHTG demonstrated the limited applicability of the MIST RCT to NHS Scotland by comparing the numbers of Scottish patients on each high-efficacy DMT with the patient numbers for prior treatment with DMTs in each arm of the RCT (SHTG 2019). SHTG concluded that it was infeasible to build a model to assess the cost effectiveness of AHSCT in people with RRMS for several reasons, including the absence of RCTs comparing AHSCT with current high-efficacy DMTs. Other factors include limited outcome data (particularly long term data) and wide variation in costs, dependent on local protocols.

To explore whether the MIST RCT is applicable to the NHS Wales context, prescribing data for primary and secondary care were requested from the Welsh Analytical Prescribing Support Unit for a list of drugs used in the management of multiple sclerosis. A comparison of DMT use in the MIST trial with prescribing in both primary and secondary care in Wales is provided in Table 9. While the drugs in table 9 are known to be used in the management of RRMS, it is not possible to identify the indication for which the drugs were prescribed within these datasets. Therefore we cannot be certain that the drugs were prescribed for RRMS.

Table 9. RRMS treatment use in Wales compared with MIST trial

RRMS treatment [brand names]	Quantity of items prescribed primary care in Wales [a], %	Quantity of items prescribed in secondary care in Wales [b], %	Patient numbers for prior treatment with DMTs at baseline (AHSCT arm/DMT arm)	Patient numbers using each DMT in DMT arm of MIST RCT[c]
Interferon beta -1a[Avonex, Rebif]	2343, 27.3%	718, 8.1%	37/50	7
Interferon beta -1b [Betaferon, Extavia]	2075, 24.1%	0	15/11	0
Glatiramer acetate [Brabio, Copaxone]	4152, 48.5%	1967, 22.1%	30/28	9
Peginterferon beta [Plegridy]	0	267, 3.0%	NR	0
Teriflunomide [Aubagio]	0	154, 1.7%	1/1[d]	1
Dimethyl fumarate [Tecfidera]	0	3,686, 41.4%	12/12	14
Natalizumab [Tysabri]	0	811, 9.1%	7/11[e]	21
Alemtuzumab [Lemtrada, Mabcampath]	0	85, 0.95%	0[f]	0
Fingolimod [Gilenya]	28, 0.3%	710, 8.0%	6/3[g]	14
Cladribine [Mavenclad]	0	102, 1.1%	NR	0
Ocrelizumab [Ocrevus]	0	409, 4.6%	0[h]	0
Mitoxantrone	Not searched	Not searched	0[i]	6

[a]Data source: CASPA. Dates: 2019-01 to 2019-10
[b]Data source: MEDUSA. Dates: 2019/2020 April until 2019/2020 September
[c]People in the DMT group were treated with DMT as deemed appropriate by their treating neurologist, with a mean of 1.3 different DMTs per person
[d] People who fail oral cholestyramine or activated charcoal clearance to decrease teriflunomide to a plasma concentration of less than 0.02µg/ml excluded
[e] People who use natalizumab within 6 months excluded
[f] People with prior treatment with alemtuzumab excluded due to increased risk of drug-related persistent lymphopenia and autoimmune disorders
[g] People with use of fingolimod within 3 months excluded
[h] Ocrelizumab was excluded as enrolment closed in 2016 before FDA licensing
[i] People with prior treatment with mitoxantrone excluded

AHSCT: Autologous haematopoietic stem cell transplantation; CASPA: ; DMT: disease modifying therapy; MEDUSA: ; MIST: ; NR: not reported; RCT: randomised controlled trial; RRMS: relapsing remitting multiple sclerosis

As shown in table 9, prescribing of the high efficacy DMT alemtuzumab is low in Wales in both primary and secondary care (zero items recorded between January and October 2019 and 85 items recorded between April and September 2019, respectively). There is slightly higher prescribing of ocrelizumab in secondary care, with 409 items recorded between April and September 2019. HTW were advised by experts that ocrelizumab is increasingly prescribed in Wales for people with RRMS, while the use of alemtuzumab is decreasing.

In the same period, 811 items of the high efficacy DMT natalizumab were recorded in secondary care. However, these figures are substantially lower than the data for the moderate efficacy drugs glatiramer acetate and dimethyl fumarate.

HTW researchers considered that the control arm of the MIST RCT is comparable with Welsh prescribing data and therefore that the trial is applicable to NHS Wales. Furthermore, the MIST RCT presented the results of a subgroup analysis of people who received natalizumab in the trial, for the outcome 'confirmed disease progression at 1 year.' Therefore, an economic analysis was undertaken using clinical data from the MIST RCT.

2. Model overview

A cost-utility analysis was undertaken to determine the cost effectiveness of AHSCT compared with DMTs for people with RRMS. In the base case, the model compares AHSCT with the DMTs used in the MIST RCT. In a sensitivity analysis, AHSCT is compared with a subgroup of people receiving natalizumab in the MIST RCT.

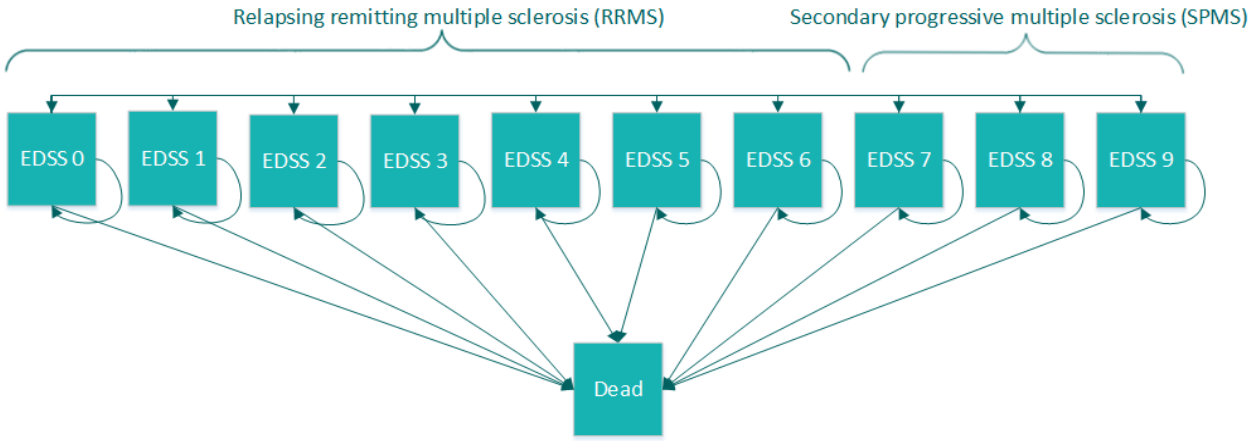
A Markov model was used to estimate costs and quality-adjusted life years (QALYs) from the UK NHS and personal social services perspective. Due to a lack of long term clinical evidence, the time horizon of the analysis was limited to five years. Costs and QALYs were discounted at 3.5% per year as recommended in the NICE reference case.

The population entering the model matched that of the MIST RCT: people with relapsing-remitting MS who experienced at least 2 relapses while receiving DMT in the prior year, and with an EDSS score of 2.0 to 6.0.

3. Model approach

The cost utility analysis uses a model structure which was adapted from a published cost utility analysis which compared cladribine tablets, alemtuzumab and natalizumab for people with RRMS with high disease activity (Hettle et al. 2018). This study was identified during a search for EDSS-specific utility data on the TUFTS database. The model comprises 11 health states representing EDSS 1.0 to EDSS 10 (death, all causes). Hettle et al. (2018) included an additional 10 states to model discontinuation of DMTs, which have not been included in this analysis, as a simplifying assumption. Categorisation of EDSS followed the approach used in Hettle et al. (2018).

Figure 1. Structure of the Markov model



EDSS: Expanded Disability Status Scale

A schematic of the model structure, adapted from Hettle et al. (2018), is shown in figure 1. In each one-year cycle of the Markov model, people are at risk of progressing to a higher EDSS state, moving to a lower EDSS (improving), remaining in the current EDSS state or death. The

probability of improving in EDSS differs across treatment arms (AHSCT or DMT), which leads to different distributions of people across the health states and differences in total costs and QALYs. In addition to modelling the effect of treatment on disease progression, the model considers the effect on relapse.

4. Clinical inputs

At model entry, the cohort was assigned to the health states according to the baseline EDSS distribution in the MIST RCT, pooling across both arms of the trial (table 10) (Burt et al. 2019). The MIST RCT reports no difference in baseline mean EDSS between the two arms. These data were obtained from the supplementary materials of the MIST RCT (Burt et al. 2019). EDSS at baseline was reported for 50/52 people included in the primary analysis in the AHSCT arm and 48/51 people in the DMT arm. There was one person with a baseline EDSS of 1 in the DMT arm of the trial and one person in each arm with an EDSS of 1.5, while the MIST inclusion criteria state that people with EDSS score of 2.0 to 6.0 are eligible.

Table 10 EDSS distribution at baseline, pooled across autologous haematopoietic stem cell therapy and disease modifying therapy arms of the MIST Randomised Controlled Trial

Health State	% at baseline	n	Distribution used for PSA
EDSS 0	0%	0	Fixed
EDSS 1-1.5	3%	3	Dirichlet
EDSS 2-2.5	33%	32	Dirichlet
EDSS 3-3.5	33%	32	Dirichlet
EDSS 4-4.5	21%	21	Dirichlet
EDSS 5-5.5	6%	6	Dirichlet
EDSS 6-6.5	4%	4	Dirichlet
EDSS 7-7.5	0%	0	Fixed
EDSS 8-8.5	0%	0	Fixed
EDSS 9-9.5	0%	0	Fixed

EDSS: Expanded Disability Status Scale; PSA: probabilistic sensitivity analysis
Source: MIST Randomised controlled trial (Burt et al. 2019)

The transition probabilities which govern how people move through the EDSS health states of the Markov model were derived from those reported in Hettle et al. (2018) (table 11). Hettle et al. (2018) report annual transition probabilities for people with age of onset of MS no less than 28 receiving 'best supportive care', which are adjusted to account for the faster progression in people with high disease activity-RRMS compared with active RRMS in EDSS states 0-6. To obtain the transition probabilities for people on DMTs, Hettle et al. (2018) applied the hazard ratio for disease progression on treatment versus placebo to the one-year rates of progression in EDSS in people receiving best supportive care. The model assumed no effect of treatment on EDSS improvement.

Table 11. Hettle et al. (2018) annual transition probabilities (%) for EDSS states (MS age of onset ≥28 years) for people receiving best supportive care, after adjustment for HDA-RRMS

EDSS From/To	0	1-1.5	2-2.5	3-3.5	4-4.5	5-5.5	6-6.5	7-7.5	8-8.5	9-9.5
0	58.3%	27.8%	9.9%	3.0%	0.6%	0.2%	0.2%	0.0%	0.0%	0.0%
1-1.5	5.8%	59.8%	22.0%	8.5%	2.3%	0.6%	0.9%	0.1%	0.0%	0.0%
2-2.5	1.6%	12.1%	50.9%	23.3%	6.2%	2.6%	3.0%	0.2%	0.1%	0.0%
3-3.5	0.6%	5.0%	12.0%	43.8%	12.6%	8.1%	16.0%	1.4%	0.5%	0.0%
4-4.5	0.2%	2.2%	6.7%	11.5%	37.7%	14.2%	23.0%	3.5%	0.9%	0.1%
5-5.5	0.1%	0.5%	2.9%	5.9%	8.7%	36.8%	37.1%	5.3%	2.6%	0.1%
6-6.5	0.0%	0.1%	0.4%	2.5%	3.1%	4.1%	67.4%	15.5%	6.2%	0.6%
7-7.5	0.0%	0.0%	0.1%	0.2%	0.7%	0.4%	11.7%	69.3%	16.1%	1.6%
8-8.5	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	1.9%	5.6%	90.3%	2.1%
9-9.5	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	0.6%	17.4%	81.8%

N.B. Cells shaded turquoise represent the annual probability that a person neither improves in EDSS or progresses, and therefore stays in the same health state
Cells shaded yellow represent the annual probability of progressing to a higher EDSS. The treatment effect for confirmed disease progression is applied for these transitions.
EDSS Expanded Disability Status Scale: ; HDA: high disease activity; RRMS: relapsing remitting multiple sclerosis
Source: Hettle et al. (2018)

The Hettle et al. (2018) transition probabilities for people with HDA-RRMS receiving best supportive care (table 11) were first converted into rates using the below formula:

$$P(t) = 1 - e^{-rt}$$

The hazard ratio from Hettle et al. (2018) for confirmed disease progression with natalizumab compared with standard care was then applied to the rates of progression, before converting back to probabilities (table 12). These treatment-adjusted transition probabilities were used in the DMT arm. To obtain the transition probabilities for people undergoing AHSCT, the hazard ratio for confirmed disease progression at one year on AHSCT compared with DMTs from the MIST trial was applied to the rates of confirmed disease progression on natalizumab. The hazard ratio for confirmed disease progression at one year was used, as in the MIST trial people in the DMT arm were permitted to crossover to the AHSCT after one year. In a sensitivity analysis, the hazard ratio for confirmed disease progression on AHSCT compared with natalizumab (MIST) was applied. In both arms, treatment was assumed to only affect the probability of progressing in EDSS, with no effect on EDSS improvement. Therefore, the transition probabilities for improvement in EDSS are those of the natural history model from Hettle et al. (2018), and remain constant in the analysis.

Table 12. Treatment effect for confirmed disease progression (1 year)

Comparison	Hazard ratio	95% Confidence Interval	Distribution for PSA	Source
Natalizumab versus placebo	0.360	0.170–0.770	Log-Normal	Hettle et al. (2018)
AHSCT versus Natalizumab	0.362	0.018 - 7.134	Log-Normal	MIST RCT (Burt et al. 2019)
AHSCT versus DMTs	0.078	0.027 - 0.228	Log-Normal	MIST RCT (Burt et al. 2019)
AHSCT: autologous haematopoietic stem cell transplantation; DMT: disease modifying therapy PSA: Probabilistic sensitivity analysis				

The model also considers the effect of AHSCT and DMT on relapse, independent of the effect of treatment on confirmed disease progression. The MIST trial reports the number of people experiencing relapse in the first year after treatment, but not the total number of relapses in each arm. Therefore the model assumes that people who experience relapse have one relapse per year. This assumption was made on the advice of clinical experts. People alive in the health states representing EDSS 0-6 experience the same probability of relapse. On the basis of the advice of clinical experts, people in EDSS 7, EDSS 8 and EDSS 9 are assumed to have progressed to SPMS and therefore do not experience relapse. This approach differs from Hettle et al. (2018), in which all people alive in the model were at risk of one or more relapses per model cycle and from Tappenden et al. (2010), in which EDSS-specific relapse rates were applied. As the time horizon of the analysis is 5 years, the annual probability of relapse is constant and is based on the number of people experiencing relapse in the MIST RCT within 1 year (table 13).

Table 13. Treatment effect for relapse (1 year)

Comparator	Percentage of people with relapse (1 year)	95% Confidence Interval	Distribution for PSA	Source
DMT (n=51)	71%	52.2%-77.2%	Beta	MIST RCT (Burt et al. 2019)
AHSCT (n=52)	1.92%	0.27%-12.9%	Beta	MIST RCT (Burt et al. 2019)
Natalizumab (n=21)	43%	20%-65%	Beta	MIST RCT (Burt et al. 2019)

AHSCT: autologous haematopoietic stem cell transplantation; DMT: disease modifying therapy; PSA: Probabilistic sensitivity analysis

No deaths were reported in either arm of the MIST RCT within five years. National Life Tables, published by the Office for National Statistics, based on UK mortality data for the years 2016-2018 were used to model all-cause mortality rates for men and women aged 35 to 100 years (Office for National Statistics 2019). The life table mortality data represent the general population, and were not adjusted for the HDA-RRMS population in this analysis. There was no assumed treatment effect on time-dependent mortality, which was fixed and applied in both arms.

The MIST RCT reports no Common Toxicity Criteria grade 4 non-haematopoietic toxicities and lists inpatient grade 3 toxicities in the AHSCT arm. It is unclear whether these inpatient toxicities occurred as part of the index hospitalisation for transplant. Separately, the MIST RCT reports post-transplant adverse events in the AHSCT arm and post-transplant adverse events in the DMT arm. The numbers of events are reported without follow-up periods. No indication is given as to the severity of the adverse events. In addition, adverse events are not reported for people who received DMTs only. For these reasons, adverse events have not been included in this analysis.

5. Cost inputs

The total cost of AHSCT comprised three components: harvesting, transplant and follow-up. People in the MIST RCT undergo peripheral blood stem cell collection. HTW researchers were advised by clinical experts that some people undergoing AHSCT require more than one attempt at harvesting, however it is unclear whether the tariff would be applied twice in these cases. As no resource use data were available in the MIST RCT, the cost of harvesting is only included once. People in the model only undergo AHSCT once.

The national average unit costs of harvesting and transplant are from the NHS Reference Costs 2018 to 2019 (NHS Reference Costs 2018/2019).The national average, lower quartile and upper

quartile unit costs for the equivalent Healthcare Resource Groups (HRGs) were taken from the NHS Reference Costs 2016/2017 in order to vary the 2018/2019 unit costs in a probabilistic sensitivity analysis (as the 2018/2019 NHS Reference Costs do not provide lower and upper quartile unit costs) (NHS Reference Costs 2016/2017). The difference between the 2016/2017 lower and upper quartiles and the 2016/2017 national average unit cost was then added to the 2018/2019 national average cost to give an estimate of the 2018/2019 lower and upper quartile unit costs.

As described above, the MIST RCT lists inpatient grade 3 toxicities in the AHSCT arm and it is unclear whether these inpatient toxicities occurred as part of the index hospitalisation for transplant. As the 2018/2019 NHS Reference Cost does not provide a Casemix Companion split (CC score) for the AHSCT 'transplant' cost, the costs of people who experience adverse events within the same hospitalisation as the transplant are assumed to be included within the national average cost given in table 14. However, the national average unit cost is not specific to the RRMS population and the proportion of people experiencing the adverse events is unlikely to match the MIST RCT data.

HTW was advised by a clinical expert of the estimated resource use associated with AHSCT in this group of patients. For the costs of follow-up, people with RRMS receiving AHSCT are assumed to have a consultant-led appointment in clinical haematology weekly until day 100, then again at six months post-AHSCT and at one year. In a previous published cost utility analysis of AHSCT versus mitoxantrone for people with SPMS, which was excluded from this evidence appraisal report, included a cost of £6,000 (cost year 2007) in addition to the tariff for AHSCT which was said to include the following components: additional baseline assessments, supplementary treatments with anti-thymocyte globulin and methylprednisolone, along with additional inpatient attendances, nine weekly cytomegalovirus (CMV) tests and treatment of CMV reactivation, where required. It is likely that the costs items listed by the clinical expert are included in the Tappenden et al. (2010) estimate, with some additional components identified by Tappenden et al. (2010). The £6,000 cost was therefore used, inflated to the 2018 cost year.

HTW was advised that after the first year, people undergoing AHSCT would continue to attend for a consultant-led appointment in clinical haematology on an annual basis. This cost is applied to those alive after AHSCT in the model. People in the AHSCT arm of the model are also assumed to incur the cost of a consultant-led non-admitted face-to-face attendance in neurology on an annual basis. The cost of an annual MRI is not included as it is expected to occur in both arms.

Table 14 Unit costs of autologous haematopoietic stem cell transplant (elective inpatient, inclusive of excess bed days)

Currency Description	Mean[a]	Lower quartile unit cost	Upper quartile unit cost	Number of FCEs	Distribution for PSA
Harvesting					
Peripheral Blood Stem Cell Harvest; day case (HRG: SA34Z)	£1,133	£665	£1,136	2,740	Gamma
Peripheral Blood Stem Cell Harvest; elective inpatient (HRG: SA34Z)	£4,831	£3,088	£6,506	224	Gamma
Proportion day case	92%	-	-	-	Dirichlet
Proportion elective inpatient	8%	-	-	-	Dirichlet
Transplant					

Currency Description	Mean[a]	Lower quartile unit cost	Upper quartile unit cost	Number of FCEs	Distribution for PSA
Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over (OPCS: XX34; HRG: SA26A)	£16,768	£9,925	£21,040	1,752	Gamma
Follow-up and additional costs					
Additional costs from (Tappenden et al. 2010)[b]	£7,289[c]	-	-	-	Fixed
Clinical Haematology: Consultant-Led, Non-Admitted Face-To-Face Attendance, Follow-Up	£168	£116	£205	1,188,366	Gamma
Neurology: Consultant-Led, Non-Admitted Face-To-Face Attendance, Follow-Up	£169	£133	£190	721,672	Gamma
[a]Reference costs are the average unit cost to the NHS of providing defined services to NHS patients in England in a given financial year. [b] Cost of additional baseline assessments, supplementary treatments with anti-thymocyte globulin and methylprednisolone, along with additional inpatient attendances, nine weekly CMV tests and treatment of CMV reactivation, where Required [c]Inflated from cost year 2007 to 2018 costs using OECD PPPs.					
Source: NHS Reference Costs 2018-2019					
FCE: finished consultant episode; HRG: healthcare resource group; OPCS: OPCS classification of Interventions and Procedures; PSA: probabilistic sensitivity analysis					

To calculate the costs of DMTs in the comparator arm, the proportions of DMT use in the DMT arm of the MIST RCT was used (table 15). The exception was mitoxantrone, which six people in the DMT arm of MIST received. The costs of mitoxantrone were excluded from the model on the advice of clinical experts. In a sensitivity analysis, everyone in the DMT arm of the model received the costs of natalizumab and the disease progression and relapse treatment effects for AHSCT compared with people who received natalizumab were applied.

The MIST RCT reports that people in the trial were managed with an average of 1.3 DMTs (Burt et al. 2019). Clinical experts described that people with RRMS are likely to switch to different DMTs after an estimated three years. As the model involves applying the costs of a basket of DMTs, it is assumed that this accounts for treatment switching. The model assumes that no one discontinues DMTs altogether, as this was not reported to have occurred in the MIST RCT.

While people in the DMT arm of the MIST trial also received other non-DMT drugs, these were received generally in by less than 5% of the people in the arm, with the exception of methylprednisolone which 75% of people received. For the purposes of the model, it is expected that these costs are accounted for by the probability of relapse in the DMT arm, which is managed using methylprednisolone. Further details on the management of relapse are given below.

As described above, as adverse events are not reported in the MIST RCT for people who received DMTs only, no costs of adverse events are included in the model.

In the AHSCT arm, HTW was advised by clinical experts that it would be unlikely that people who progress following AHSCT would be offered rescue therapy with DMTs. However, in a sensitivity

analysis, people in EDSS 2 to EDSS 6 were modelled to receive the same basket of DMTs as those in the DMT arm.

Table 15 Management with DMTs in DMT arm of MIST RCT

	Proportion of DMT use	Number of people receiving each DMT	Distribution for PSA
Natalizumab	32%	21	Dirichlet
Dimethylfumarate	21%	14	Dirichlet
Fingolimod	21%	14	Dirichlet
Glatiramer acetate	14%	9	Dirichlet
Interferon beta-1a	11%	7	Dirichlet
Teriflunomide	2%	1	Dirichlet

DMT: disease modifying therapy; PSA: probabilistic sensitivity analysis
Source: (Burt et al. 2019)

The total cost of management with each DMT comprises the cost of drug acquisition, administration and monitoring. Acquisition costs are from the British National Formulary and administration and monitoring costs are from the NHS Reference Costs 2018/2019. Inputs and detail regarding assumptions made about resource use are provided in table 16. These costs are applied throughout the model in the DMT arm, to everyone in EDSS 0-6. In EDSS 7+, people are assumed to have SPMS. In the base case, 50% of people are assumed to receive an SPMS diagnosis, as clinical experts advise that it is difficult to diagnose in this population. Therefore, 50% of people continue to receive the basket of DMTs, while the other 50% are managed for SPMS with interferon beta-1a (table 15). In probabilistic sensitivity analysis, the percentage of people receiving a diagnosis of SPMS is varied uniformly between 50% and 100%. In the base case, people in the AHSCT arm do not receive rescue DMTs. Therefore, people who progress to EDSS 7 are all assumed to receive an SPMS diagnosis and are all managed with interferon beta-1a. In a sensitivity analysis, people who progress after AHSCT receive rescue DMT, and so the assumptions for SPMS diagnosis from the DMT arm apply.

Table 16. Unit costs of DMTs

	Mean unit cost	95% CI	Cost per year	Distribution for PSA	Notes
Natalizumab					
Acquisition[a]: Natalizumab 300mg/15ml	£1,130	-	£14,690	Fixed	4 weekly 300mg/15ml infusions[c]
Administration[b]: Day case: Medical Care of Patients with Multiple Sclerosis (HRG: AA30)	£612	-	£7,959	Gamma (costs); Dirichlet (CC proportions)	13 x Day case attendance per year[c]: Medical Care of Patients with Multiple Sclerosis. Weighted average by CC score (HRG AA30 C-F). CC proportions varied in PSA using dirichlet distribution.
Monitoring[b]: Magnetic Resonance Imaging Scan of One Area, without Contrast, 19	£121	£90-£162	£48	Gamma	Monitoring (viral test every 6 months[d]) undertaken as part of day case hospitalisation for administration[d]. 20% of people assumed to be high risk and to require an MRI every 4 months[d]. As people in both arms
years and over					assumed to require MRI, 2 additional MRIs included for 20% of people on Natalizumab. Varied between 20%-30% in PSA using uniform distribution
		Total	£22,698		
Dimethylfumarate					
Acquisition[a]: Dimethylfumarate 120mg	£2.12	-	£3066 (year 1) £3095 (year 2+)	Fixed	Year 1: Initially 120mg twice daily for 7 days, then 240mg twice daily[c] Year 2+: 240mg twice daily[c]
Administration	£0	-	£0	Fixed	Oral medicine- assume no administration costs[d]
Monitoring[b]: Non-admitted, face-to-face neurology attendance. Non-consultant led	£115	£58-£131	£461	Gamma	3 monthly blood tests in outpatient clinic[d]
		Total	£3,527 (year 1) £3,557 (year 2)		
Fingolimod					
Acquisition[a]: Fingolimod 0.5mg	£53		£19,163	Fixed	0.5mg once daily[c]
	Mean unit cost	95% CI	Cost per year	Distribution for PSA	Notes

Administration[b]: Day case: Medical Care of Patients with Multiple Sclerosis (HRG: AA30)	£612 £0	-	£612 (year 1) £0 (year 2)	Gamma (costs) Dirichlet (CC scores) Fixed (self-administration)	Year 1: One daycase admission initially, then no administration costs[d] Year 2: No administration costs[d]
Monitoring[b]: Non-admitted, face-to-face neurology attendance. Non-consultant led	£115	£58-£131	£461	Gamma	3 monthly blood tests in outpatient clinic[d]
		Total	£20,236 (year 1) £19,623 (year 2)		
Interferon beta-1a					
Acquisition[a]: Avonex 30µg/0.5ml	£164	-	£8,502	Fixed	30 micrograms 0.5ml solution once a week and pen after patient is established[c]
Administration[b]: Day case: Medical Care of Patients with Multiple Sclerosis (HRG: AA30)	£612 £0	-	£612 (year 1) £0 (year 2)	Gamma (costs) Dirichlet (CC scores) Fixed (self-administration)	Day case admission in year 1, then self-administered[d]
Monitoring[b]: Non-admitted, face-to-face neurology attendance. Non-consultant led	£115	£58-£131	£461 (year 1) £230 (year 2)	Gamma	Year 1: Outpatient clinic every 3 months[d] Year 2: outpatient clinic every 6 months[d]
		Total	£9,576 (year 1) £8,733 (year 2)		
Teriflunomide					
Acquisition[a]: Teriflunomide 14mg	£37	-	£13,538	Fixed	14 mg once daily[c]
Administration	£0	-	£0	Fixed	Oral medicine- assume no administration costs[d]
Monitoring[b]: Non-admitted, face-to-face neurology attendance. Non-consultant led	£115	£58-£131	£2,249 £1,499	Gamma	Year 1: Outpatient clinic every 2 weeks for 6 months and then 4 weekly thereafter[d] Year 2: outpatient clinic every 2 weeks[d]
		Total	£15,787 (year 1) £15,037 (year 2)		

CC score: Casemix Companion; HRG: healthcare resource group: PSA: probabilistic sensitivity analysis
[a]Source: British National Formulary
[b]Source: NHS Reference Costs 2018/2019
[c]Resource use estimate from British National Formulary
[d]Resource use estimate provided by clinical experts

For the costs of management of an acute relapse, an assumption was made based on clinical expertise that 5% of people require hospitalisation, while the remaining 95% of people can be managed at home. The costs and resource use assumptions are provided in table 17.

Table 17. Unit costs of relapse

	Mean	Range	FCE	% CC score	Distribution for PSA
Probability of hospitalisation for an acute relapse[c]	5%	5%-10%	-		Uniform
Probability of management at home for an acute relapse[c]	95%	90%-95%	-		Uniform
Non-elective Long Stay: Medical Care of Patients with Multiple Sclerosis, with CC Score 8+[a]	£5,685	£3,710-£6,703	1,030	38%	Gamma (costs) Dirichlet (CC score)
Non-elective Long Stay: Medical Care of Patients with Multiple Sclerosis, with CC Score 5-7[a]	£3,570	£2,478-£4,434	634	25%	Gamma (costs) Dirichlet (CC score)
Non-elective Long Stay: Medical Care of Patients with Multiple Sclerosis, with CC Score 2-4[a]	£2,534	£2,287-£3,366	719	20%	Gamma (costs) Dirichlet (CC score)
Non-elective Long Stay: Medical Care of Patients with Multiple Sclerosis, with CC Score 0-1[a]	£2,342	£1,807-£2,915	480	17%	Gamma (costs) Dirichlet (CC score)
Non-elective Short Stay: Medical Care of Patients with Multiple Sclerosis, with CC Score 8+[a]	£554	£198-£580	313	27%	Gamma (costs) Dirichlet (CC score)
Non-elective Short Stay: Medical Care of Patients with Multiple Sclerosis, with CC Score 5-7[a]	£554	£343-£651	418	27%	Gamma (costs) Dirichlet (CC score)
Non-elective Short Stay: Medical Care of Patients with Multiple Sclerosis, with CC Score 2-4[a]	£481	£331-£593	660	23%	Gamma (costs) Dirichlet (CC score)
Non-elective Short Stay: Medical Care of Patients with Multiple Sclerosis, with CC Score 0-1[a]	£497	£378-£559	705	24%	Gamma (costs) Dirichlet (CC score)
Proportion long stay[a]	58%	-	2,863	-	Dirichlet
Proportion short stay[a]	42%	-	2,096	-	Dirichlet
Total cost (hospitalisation for acute relapse)[a]	£2,588				
Management at home with steroids: methylprednisolone 500mg once daily for 5 days[b]	£60	-	-	-	Fixed
Non-admitted, face-to-face neurology attendance. Consultant led	£169	£133-£190	721,672	-	Gamma
Total cost (management of acute relapse at home)	£229				

[a]Reference costs *are the average unit cost to the NHS of providing defined services to NHS patients in England in a given financial year.*

Source: [a]NHS Reference Costs 2018/2019, [b]British National Formulary
[c]Assumption provided by clinical experts

CC: Casemix companion; FCE: finished consultant episode; HRG: healthcare resource group; PSA: probabilistic sensitivity analysis

For EDSS-specific costs, those used in the Hettle et al. (2018) cost utility analysis were inflated to 2018 costs (table 18). Hettle et al. (2018) obtained the costs from a second study (Hawton & Green 2016) and state that these costs comprise direct costs including visits to healthcare and social work professionals and the use of rehabilitation and respite services estimated through patient self-assessment. These health state costs were chosen for this analysis as they do not include the costs of management with DMTs, which could therefore be applied differentially between the AHSCT and DMT arms of the model.

Table 18. Health State Costs

Health State	Cost	Standard Error	Distribution
EDSS 0	£1,098	£290	Gamma
EDSS 1.0	£980	£174	Gamma
EDSS 2.0	£771	£95	Gamma
EDSS 3.0	£720	£84	Gamma
EDSS 4.0	£1,079	£114	Gamma
EDSS 5.0	£1,083	£124	Gamma
EDSS 6.0	£1,404	£97	Gamma
EDSS 7.0	£1,416	£186	Gamma
EDSS 8.0	£3,574	£409	Gamma
EDSS 9.0	£3,574	£409	Gamma
Dead	£0		Fixed
Source: Hettle et al. (2018) Costs were inflated from 2016 to 2018 cost year using OECD PPPs.			
EDSS: Expanded Disability Status Scale			

6. Quality of life inputs

Quality of life measured using SF-36 is reported by the MIST RCT (Burt et al. 2019). However, as EDSS-specific utilities were not available, an alternative source of utility values was used. In the cross-sectional study by Orme et al, 2,048 responses to the EQ-5D questionnaire from people with MS in the UK were evaluable (Orme et al. 2007). Participants in Wales received 5% of all questionnaires in the study. Utilities were assigned using the EQ-5D UK value set. This study was selected as the source for utility values above other studies, as the study provides utility data for all health states, and the utility decrement associated with recent relapse (table 19). The duration of acute relapse used in the model is also given in table 18. In this set of utility values, in several instances lower EDSS are associated with lower utility values than higher EDSS. For example, the utility for EDSS 3.0 is 0.571 while the utility for EDSS 4.0 is 0.608. It is also important to note that EDSS 8.0 and 9.0 have negative utility values, which implies a utility worse than death. In probabilistic sensitivity analysis, the utilities of EDSS 8.0 and 9.0 are varied using a beta distribution and confined to negative values.

Table 19. Utility inputs

Health State	Utilities	Alpha	Beta	Distribution
EDSS 0	0.868	24.30	3.70	Beta
EDSS 1.0	0.799	120.65	30.35	Beta
EDSS 2.0	0.704	126.72	53.28	Beta

EDSS 3.0	0.571	43.97	33.03	Beta
EDSS 4.0	0.608	117.34	75.66	Beta
EDSS 5.0	0.513	165.70	157.30	Beta
EDSS 6.0	0.460	182.16	213.84	Beta
EDSS 7.0	0.299	62.79	147.21	Beta
EDSS 8.0	**-0.05**	**8.25**	**156.75**	**Beta**
EDSS 9.0	-0.196	3.14	12.86	Beta
Dead	0	-	-	Fixed
Relapse (decrement)	-0.071	42	550	Beta
Relapse duration	5 weeks	(range 1 week – 3 months)	-	Uniform
Source: Orme et al. (2007)				
EDSS: Expanded Disability Status Scale				

7. Base case results

The results of the base case analysis is presented in table 20, which shows the total and incremental costs and QALYs over the time horizon (presented on a per patient basis) as well as the incremental cost effectiveness ration (ICER). It can be seen that treatment with ASHCT was found to be more effective and less costly than standard treatment with DMTs and was therefore dominant.

Table 20. Base case results

Treatment strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
DMT	£73,496	-	2.94	-	-
AHSCT	£31,087	-£42,409	3.15	0.21	Dominant

8. Deterministic sensitivity analysis results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter was changed, the model was re-run and the new cost-effectiveness result was recorded. This form of analysis is a useful way of exploring alternative assumptions and determining the key drivers of the model results. The results of the deterministic sensitivity analysis are presented in table 21.

Table 21. Deterministic sensitivity analysis results

Modelled scenario	ICER (cost per QALY)
Base case	Dominant
Comparison against natalizumab only (with disease progression and relapse rate from MIST trial)	Dominant
Comparison against natalizumab only (with disease progression and relapse rate from Hettle et al. (2018))	Dominant
No acute relapse events	Dominant
Comparison against natalizumab without acute relapse events	Dominant

No improvements in EDSS permitted within transition probabilities	Dominant
DMT rescue in stem cell arm after progression to EDSS 2	Dominant
No improvements in EDSS permitted within transition probabilities and DMT rescue in stem cell arm after progression to EDSS 2	£38,359
Comparison against natalizumab with DMT rescue in stem cell arm after progression to EDSS 2	Dominant
Comparison against natalizumab with no improvements in EDSS permitted within transition probabilities and DMT rescue in stem cell arm after progression to EDSS 2	£2,741
Utility values from Hettle et al. (2018)	Dominant
AHSCT cost = £30,000	Dominant
Welsh-specific cost for AHSCT = £28,000	Dominant

The conclusion of the analysis was not found to change in most of the modelled scenarios with AHSCT found to be more effective and less costly than standard care and therefore dominant. The notable exceptions were the scenarios in which improvements in EDSS were not permitted within the transition probabilities and DMT rescue was introduced following progression to EDSS 2. In these scenarios, AHSCT was still found to be more effective but it was also found to be more costly. When compared against all DMTs, the ICER was found to be £38,359 per QALY indicating that AHSCT was not cost-effective as the ICER was above the threshold of £20,000 per QALY. When compared against natalizumab only, the ICER was found to be £2,741 per QALY indicating that AHSCT was cost-effective as the ICER was below the threshold of £20,000 per QALY. In the scenarios where improvement in EDSS is not permitted, the mean EDSS scores as predicted by the model are higher than those reported in the AHSCT arm of the MIST RCT in each of years 1-5. When EDSS score improvement is permitted in the transition probabilities, the mean EDSS score as predicted by the model matches more closely the mean EDSS in the AHSCT arm of the MIST RCT.

A threshold analysis was carried out to determine the cost per year for management with DMTs at which AHSCT would no longer be cost effective at the £20,000 per QALY gained threshold. Under the assumptions of the base case, if the total annual cost (including acquisition, administration and monitoring) of DMTs falls below £4,339 per person, then AHSCT is no longer cost effective over a five year time horizon.

A second threshold analysis was carried out on the up-front cost of AHSCT. Under the assumptions of the base case, the total cost of AHSCT would need to increase to £72,056 to no longer be cost effective at the £20,000 per QALY gained threshold over a five year time horizon.

9. Probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using an ICER scatterplot and cost-effectiveness acceptability curve (CEAC). The ICER scatter plot shows the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graph shows the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

The ICER scatterplot in figure 2 shows that all of the results reside in the south east quadrant indicating that AHSCT is more effective and less costly than standard care with DMTs in all modelled scenarios. The CEAC in figure 3 shows that the probability of AHSCT and DMTs being cost-effective remains constant as the cost-effectiveness threshold increases. At a threshold of £20,000 per QALY, AHSCT was found to have a 100% probability of being cost-effective while standard care with DMTs had a 0% probability of being cost-effective.

Figure 2. ICER scatterplot for analysis comparing AHSCT to standard care with DMTs

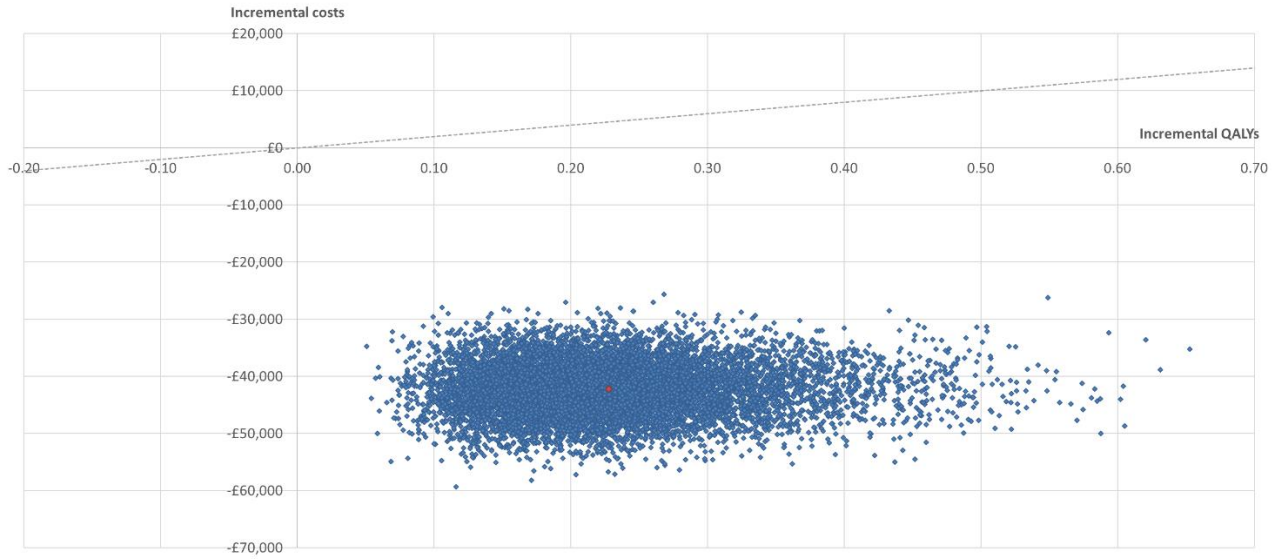
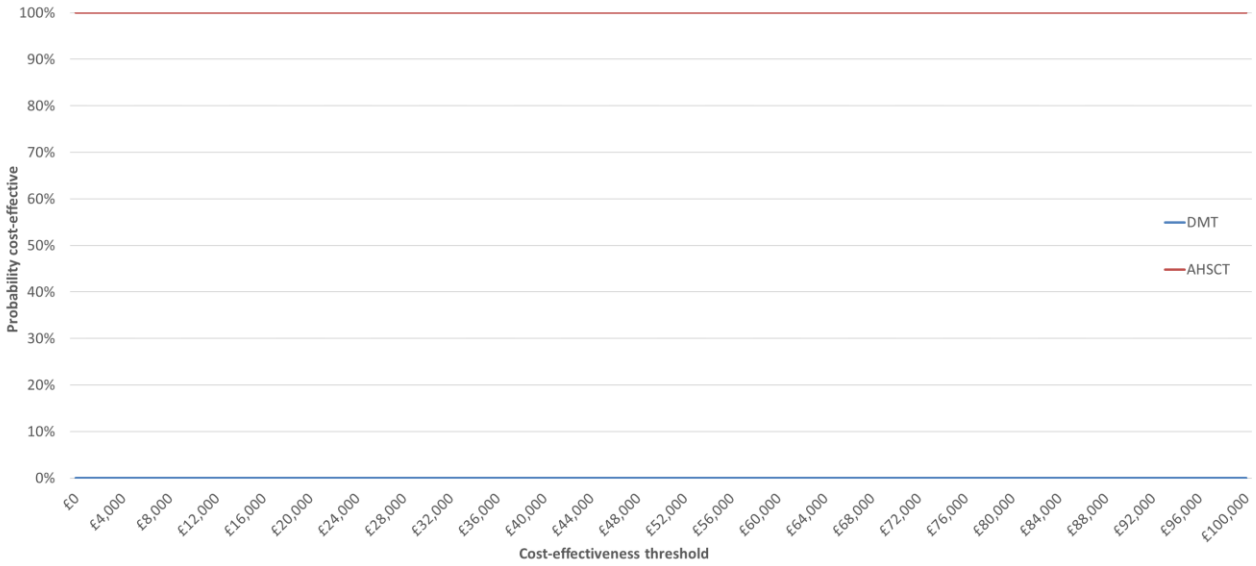


Figure 3. CEAC for analysis comparing AHSCT to standard care with DMTs



10. Discussion

The results of the cost utility analysis suggest that, in comparison to DMTs used in the MIST RCT, AHSCT is dominant (more effective and less costly) in people with highly active RRMS. At a threshold of £20,000 per QALY gained, AHSCT was found to have a 100% probability of being cost-effective while standard care with DMTs had a 0% probability of being cost-effective in the base

case. This result is likely explained by the high ongoing costs of DMTs compared with the up-front cost of AHSCT, combined with the high effectiveness of AHSCT as reported in the MIST RCT.

In a scenario where AHSCT was compared with the higher efficacy DMT natalizumab, the result did not change and AHSCT remained dominant. In this scenario, the costs of natalizumab were applied in the DMT arm and the relative effectiveness of AHSCT was calculated using a hazard ratio for a subgroup of people who received natalizumab compared with AHSCT in the MIST RCT. AHSCT remained dominant because, despite being more effective relative to other DMTs, natalizumab is also more costly than other DMTs.

In further scenarios where rescue with DMT therapy after one year was introduced for people who progressed to EDSS 2 following AHSCT, AHSCT remained dominant over both standard of care with a basket of DMTs and natalizumab alone. Clinical experts advise HTW that it is unlikely that rescue with DMTs would be offered to people who progress after AHSCT.

A threshold analysis was carried out on the up-front cost of AHSCT. Under the assumptions of the base case, the total cost of AHSCT would need to increase to £72,056 to no longer be cost effective at the £20,000 per QALY gained threshold over a five year time horizon. Experts advise that the cost of AHSCT in Wales is £28,000.

This analysis has several limitations, which are explored below.

This cost utility analysis was based upon the MIST RCT and so shares its limitations (Burt et al. 2019). Since the MIST RCT was established, experts advise that fewer injectables are used in current practice (interferon/glatiramer) and cheaper oral DMTs are increasingly used as first line. Welsh prescribing data (table 8) shows that interferon and glatiramer comprise 30.2% of prescribing in secondary care whereas dimethyl fumarate comprises 41%. It should be noted that these data are not specific to the highly-active RRMS population.

To address this issue, a threshold analysis was carried out to determine the cost per year for management with DMTs at which AHSCT would no longer be cost effective at the £20,000 per QALY gained threshold. The assumptions of the base case were applied, including that the effectiveness of DMTs is based on people receiving a basket of DMTs which includes the high efficacy DMT natalizumab (£22,698 per person per year). Under these assumptions, if the total annual cost (including acquisition, administration and monitoring) of DMTs falls below £4,339 per person, then AHSCT is no longer cost effective over a 5 year time horizon. The annual costs of management with different DMTs are provided in table 15. The injectable DMTs interferon and glatiramer cost £9,578 and £7,087 per person per year, whereas the oral drugs dimethylfumarate and teriflunomide cost £3527 and £15,787 per person per year, respectively.

Experts advise that in current practice people with rapidly evolving severe MS receive higher efficacy drugs. The MIST RCT omitted ocrelizumab as it was not licensed at the time of recruitment and excluded those who had previously been treated with alemtuzumab (Burt et al. 2019).. This analysis included sensitivity analyses where AHSCT was compared with natalizumab, using the results of a subgroup analysis of the MIST RCT which considered those managed using natalizumab (n=21). It should be noted that people in the MIST RCT were not randomised between natalizumab and other DMTs. To establish the cost effectiveness of AHSCT compared with the high efficacy DMTs natalizumab, ocrelizumab and alemtuzumab, the results of future trials awaited. HTW were advised by experts that ocrelizumab is increasingly prescribed in Wales for people with RRMS, while the use of alemtuzumab is decreasing.

While people with rapidly evolving MS receive higher efficacy drugs as first line in current practice, experts advise that there is uncertainty whether people who do not have rapidly evolving MS should first be offered moderate efficacy DMT and stepping up only if there is breakthrough activity, or offered high efficacy DMTs at the outset. Some participants in the MIST

RCT were escalated directly to AHSCT from interferon/glatiramer. While this escalation may not reflect current practice, the results of this analysis indicate that AHSCT is cost effective for people meeting the inclusion criteria of the MIST RCT.

In the DMT arm of the model, a weighted average cost was applied for the cost of DMTs, based upon the DMT use in the MIST RCT. The exception to this was mitoxantrone, which was not included as clinical experts advised that the drug is not in use in the UK. However, it was not possible to exclude mitoxantrone from the effectiveness data. People in the MIST RCT received an average of 1.3 DMTs and clinical experts advise that in practice people are managed using the same DMT for an average of three years. For the purposes of this model, we apply the proportions of DMT use from the MIST RCT constantly throughout the time horizon of the model.

In the DMT arm, the same 'basket' of DMTs was applied for each EDSS state up to EDSS 6. In EDSS 7, 50% of people are assumed to receive a diagnosis of SPMS and to discontinue from the basket and receive interferon beta-1a only. Discontinuation from DMTs is not otherwise modelled. The DMT 'basket' is applied in the remaining 50% of people. Clinical experts felt that this assumption reflects how difficult it is to diagnose SPMS in this group of people. As people in the AHSCT arm in health states EDSS 0-6 do not receive DMTs in the base case, people progressing to EDSS 7 were all assumed to receive management for SPMS. In the scenarios where rescue therapy with DMTs was introduced for people in EDSS 2 to EDSS 6 (applied after year 1 in the model) in the AHSCT arm, the same assumptions surrounding SPMS management were applied in both the AHSCT and DMT arm.

The MIST RCT reports adverse events following AHSCT (Burt et al. 2019). There were no Common Toxicity Criteria grade 4 non-haematopoietic toxicities. It is unclear whether the 'inpatient grade 3 transplant toxicities' in the AHSCT arm occurred during the index hospitalisation for transplant. As the NHS Reference Cost for AHSCT is not broken down by CC score, we considered that adverse events would be incorporated into this cost.

The MIST RCT also reports post-transplantation infections in the AHSCT arm and post-transplantation infections adverse events in the DMT arm, but not adverse events for people who received DMTs and did not go on to receive AHSCT. In addition, the severity of these adverse events is not reported. For these reasons, adverse events have not been included in this analysis.

The MIST RCT reports acute relapse as the number of patients with relapse and not the number of acute relapses per person. As such, the model assumes that the people who experience acute relapse experience one per year, on the advice of clinical experts. We assume that the same probability of acute relapse applies to each EDSS health state up to EDSS 6. People in EDSS 7+ do not experience acute relapse as they are assumed to have SPMS. The treatment effect of AHSCT compared with DMTs on acute relapse rate is assumed to be constant over time.

The NHS Reference Cost for AHSCT is a generic cost covering all people undergoing AHSCT for different indications. Clinical experts expect that the length of stay for people with RRMS may differ from people with malignant conditions. As the most recent NHS Reference Costs (2018/2019) do not record length of stay, the face validity of the use of this cost could not be assessed by clinical experts. However a threshold analysis on the cost of AHSCT found that the total cost would need to increase to £72,056 to no longer be cost effective at the £20,000 per QALY gained threshold.

Finally, the MIST RCT reports that small proportions of people (≤2%) in the DMT arm received several other non-DMT treatments. These were not included in the model. Methylprednisolone was used by 75% of people in the DMT arm, however this is largely accounted for in the model in the management of acute relapse (which was experienced by 71% of people in the DMT arm in year 1).