NHS England

Clinical Commissioning Policy Proposition: Allogeneic Haematopoietic Stem Cell Transplantation for adults with sickle cell disease

Prepared by NHS England Specialised Services Clinical Reference Group for Blood and Marrow Transplant and Haemoglobinopathies

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1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About allogeneic haematopoietic stem cell transplantation for adults with sickle cell disease

Sickle cell disease (SCD) is an inherited disease affected around 12-15,000 individuals in the UK. It causes a lifelong anaemia, episodes of severe pain and other problems including an increased risk of stroke, renal failure, heart and lung problems and leg ulcers. It is associated with a reduced life expectancy, severe chronic health problems and reduction in quality of life. Allogenic haematopoietic stem cell transplantation (allo-HSCT) is the only currently available therapy that can cure sickle cell disease. It is currently offered to children, but not adults. The clinical effects of SCD are variable but those with severe sickle cell disease will require ongoing treatments and frequent hospital admissions. Allogeneic stem cell transplantation is a potential cure for sickle cell disease.

About current treatments

Current treatments are supportive rather than curative. They include simple treatments such as long-term antibiotics to prevent infection, preventative vaccines and pain relief for the acute pain episodes. Apart from supportive measures there

are only two therapies available for sickle cell disease. These are hydroxycarbamide and long-term blood transfusions. Hydroxycarbamide is the only licensed medication; this reduces the incidence of pain episodes and the incidence of some of the other complications (e.g. acute chest syndrome). Hydroxycarbamide has several side effects including reduction of blood counts and some patients are not able to tolerate it or do not respond to it. Some patients are treated with long term blood transfusion therapy; this is the best treatment to prevent strokes but has many side effects. Some patients do not tolerate blood transfusion.

About the new treatment

The only curative therapy currently available for patients with SCD is allo-HSCT. It is being offered to children with signs of severe SCD, but this therapy is not available for adults. It involves treating the recipient with chemotherapy to destroy their own bone marrow stem cells. The recipient will then receive donor stem cells which replace their blood cells with donor blood cells. The donor blood cells do not cause sickle cell disease and therefore the patient can be cured.

The best results are if the donor is a brother or sister of the recipient and has a fully matched bone marrow stem cell type (**sibling**).

What we have decided

NHS England has carefully reviewed the evidence to treat severe adult sickle cell disease with allo-HSCT.

We have concluded that there is enough evidence to consider making treatment available for patients with severe sickle cell disease with a related donor that is fully HLA matched to the recipient (**sibling)**

However, at this time have also concluded that there is not enough evidence to make the allo-HSCT available for patients with severe sickle cell disease using, a matched donor who is not related to the recipient (**matched unrelated donor)** or a related donor (this may be sibling, parent, child) that is half matched to the recipient **(haplodientical)**

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission stem cell transplant for adults with sickle cell disease.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether allogeneic haematopoietic stem cell transplantation for adults with sickle cell disease will be routinely commissioned will made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Sickle cell disease (SCD) is an inherited disease, characterised by a lifelong anaemia and intermittent episodes of severe acute pain (the sickle 'crisis'). It is also associated with other acute complications including stroke, acute chest syndrome, priapism and an increased risk of infection. In addition, it is associated with chronic multi-organ dysfunction including chronic pulmonary disease, pulmonary hypertension, chronic renal disease, progressive cerebral ischaemic damage, eye complications and chronic bony damage.

In the UK SCD is diagnosed as part of the newborn screening programme and individuals are entered onto long term medical follow up, including infection prevention and screening for chronic complications. The outcomes of SCD are very variable.

Intervention:

Severe SCD is currently commissioned for sibling and haploidentical allogeneic haematopoietic stem cell transplantation in children.

Previously it has been thought that allogeneic transplantation would not be suitable for adults who may have more co-morbidities and therefore not tolerate the procedure. Recent improvements in transplant protocols that make them suitable for adults now mean this option can be considered. The rationale for proposing allogeneic stem cell transplantation for adults is to provide a curative option for those people with severe disease in whom other treatments have failed or have not been tolerated.

Access to allo-HSCT can be divided by donor type and these will be considered separately as the outcomes from each type vary.

1) HLA matched sibling HSCT: This is associated with the best survival figures and the lowest rates of adverse outcomes (rejection and GVHD). The outcomes following this type of HSCT are better than outcomes with standard care for those with severe SCD. Only about 20% of patients will have a HLA matched sibling donor and will be able to have this type of HSCT
2) Haploidentical HSCT: This usually uses stem cells from a parent or a non-HLA matched sibling HSCT. Most people will therefore have a donor. It is potentially associated with higher rates of rejection and GVHD than HLA matched sibling HSCT. If the transplant is rejected the patient continues to have sickle cell disease. There is currently insufficient evidence to support this type of transplant as standard care for those with severe SCD.
3) Matched unrelated donor HSCT. This type of transplant is associated with worse outcomes and more adverse outcomes in terms of GVHD than HLA matched sibling HSCT. There is currently insufficient evidence to support this type of transplant as standard care for those with severe SCD

Clinical indication for HSCT

HSCT should only be considered in those adults with severe SCD where the benefits outweigh the risks. The reasons for considering HSCT are that

- SCD is associated with a reduced survival
- SCD is associated with severe chronic morbidity
- Current treatments are not effective in some patients

Indications for HSCT

HSCT should be offered to the sub-group of adults with predicted worse outcomes and in whom survival is significantly reduced. This includes those with additional co-morbidities e.g. stroke, pulmonary hypertension, severe disease who are likely to experience high rates of mortality (25%) over a 10-year period as identified by Elmariah et al (2014).

Allogeneic HSCT with a matched sibling donor is recommended in adults with severe SCD who have predicted poor outcomes. This includes patients with a:

- History of >= 3 severe pain crises or other acute complications per year despite institution of supportive care measures (optimal treatment with hydroxycarbamide (HC) or transfusion therapy). Other acute complications would include acute hepatopathy or splenic sequestration or acute priapism
- Recurrence of acute chest syndrome despite optimum treatment with hydroxycarbamide (HC) or transfusion therapy
- Clinically significant neurologic vascular event or deficit lasting over 24 hours and confirmed radiologically (i.e. stroke) or progressive cerebral vasculopathy
- Administration of regular transfusion therapy, either by simple transfusion or exchange transfusion with the aim to prevent severe sickle complications by maintaining a low HbS%. Severe sickle complications include a history of >= 2 chest syndromes, >= 3 painful crises or severe recurrent priapism
- Patients assessed as requiring transfusion but with red cell allo-antibodies/very rare blood type, rendering it difficult to continue/commence chronic transfusion
- Patients requiring hydroxycarbamide/transfusion for treatment of SCD complications who cannot tolerate either therapy due to significant adverse reactions
- Established end organ damage relating to SCD including but not limited to progressive sickle vasculopathy and hepatopathy.

In addition, the patient should not meet any of the standard exclusion criteria for HSCT.

This list of indications for HSCT in adults has been adapted from the current UK Paediatric BMT Group Indications (bsbmt.org/indications-table.) It is also based on the criteria used in previous trials, and publications. Further evidence is presented below. In Gluckman et al (2017) most patients had indications of stroke, acute chest syndrome, and recurrent vaso-occlusive disease. In Ozdogu et al (2018) Patients were evaluated for transplant indications based on the SCD high-risk group criteria of the bone marrow transplantation list of the Social Security Institution of Turkey (https://organ.saglik.gov.tr/). All the patients within the Hsieh et al (2014) study were patients with severe disease. The baseline characteristics of the study participants are well described in the paper with all indications and comorbidities tabulated, including numbers of vaso-occlusive crisis, central nervous system disease, strokes and silent infarctions, stenotic or irregular arteries, transient ischemic attack, and acute chest syndrome. 43% of patients had 3 indications with at least 1 comorbid condition; 30% of patients had 2 indications with at least 1 comorbid condition, and 7% of patients had 1 indication with at least 1 comorbid condition. These descriptions are contained within the papers referenced in the Evidence Review.

The NHSE review of Haemoglobinopathy services has recommended that a National Haemoglobinopathy Panel which is multidisciplinary is set up. This should be introduced by January 2020. Part of the role of this National Haemoglobinopathy Panel will be to provide expert opinion on complex cases and when new therapies should be recommended. The Service Specification recommends that patients should be discussed at the National Haemoglobinopathy Panel before referral for HSCT to obtain constant and equitable referral patterns. This will ensure national review of all referrals for HSCTs.

In summary, the results of sibling-HSCT in adults show survival of 81-100%. For adults with severe SCD 10 year survival is less than 75%. Therefore, survival with HSCT is better than survival with current standard care

4 Definitions

Sickle Cell Disease: Sickle Cell Disease (SCD) is an inherited blood disorder which affects the red blood cells. Those affected have an abnormal haemoglobin, the protein in red blood cells which is important in oxygen transportation. Those affected have intermittent severe pain episodes, anaemia and other complications include infection, stroke and organ dysfunction.

Allogeneic Haematopoietic stem cell transplantation (HSCT) (also known as BMT): A procedure which replaces the patient's own blood stem cells and immune system with those from a healthy donor, enabling the establishment of normal blood and immune system functions.

Donor Types:

Sibling: sibling related donor that is fully matched to the recipient

Matched unrelated donor: donor is matched but not related to the recipient

Haploidentical: related donor (this may be sibling, parent, child) but half matched to the recipient

5 Aims and Objectives

This policy proposition considered:

- NHS England's position on commissioning Allogeneic Haematopoietic Stem Cell Transplant for Sickle Cell Disease for adults

The objectives were to:

- Specify the clinical indications and donor type for which allogeneic HSCT will be commissioned routinely by NHS England for adult patients with Sickle Cell Disease
- Provide equitable access to allo-HSCT for adult and paediatric patients with sickle cell disease which will result in improved clinical outcomes and

wellbeing for patients suitable for allo-HCST, at the same time as reducing variations in clinical practice

6 Epidemiology and Needs Assessment

As an inherited disease SCD is more common in particular ethnic backgrounds (Black African, Black Caribbean, Arab-Indian): in England, 61% of those screened within the national newborn screening programme and found to be likely positive were from Black African background, despite representing only 4% of all births (Streetly 2010). Those of Black Caribbean or any Black background were also among the highest incidence. Those of any White background had the lowest likelihood of being screened positive.

The annual incidence of SCD is estimated at 275,000 births per year globally (Modell, 2008). More recent data suggests that there are approximately 12,500 to 14,000 people in the UK living with SCD, equivalent to around 1 in 5,100 to 1 in 4,600 people nationally (WMQRS 2016, Dormandy 2017). 1317 infants with SCD were born between September 2010 and August 2015 (263 infants per year) (Streetly 2018).

The clinical outcomes of SCD are variable, but SCD is associated with reduced survival and significant chronic morbidity.

Reduced Survival:

Evidence shows reduced survival in adults with SCD and that patients with frequent pain episodes or other co-morbidities are more likely to die early.

One recent cohort study of 534 adults with SCD showed 25% mortality at the end of the 10 year study under standard care (Elmariah et al 2014). Mortality was higher among those having over 4 pain crisis a year or with a higher organ severity score: these would be the patients eligible for HSCT under this policy proposal. Thus, even with the worse estimation of 81% survival with HSCT in adults, this is already better than survival with current standard care.

Another retrospective 10 year single centre study of 712 showed that 43 patients died (6%) during the study at a median age of only 42 years (IQR 31-48 years). Further

statistical analysis estimated a median survival of 67 years but this included patients with variability of disease and masked the poor outcomes in those with severe disease (Gardner et al 2016). We note that this analysis predicted a 90% survival to 40 years, and 80% survival to 51 and 70% survival to 60 years. Therefore 20% of the cohort were expected to die by the age of 51 years and 10% were expected to die by 40 years. This study also showed that patients with severe disease were most likely to die.

Indicators of severe disease included those with increased rates of admission to hospital, with low baseline oxygen saturations, abnormal liver function and with abnormal renal function. In other words, patients who fulfil the criteria for severe disease and who would be eligible for HSCT have a poor prognosis.

Other papers have also shown a reduced median life expectancy of 35- 45 years (Maitra et al Haematologica 2017, Lanzkron et al 2013 Pub Health Revs, Hassel 2010).

Those with milder disease and who receive early intervention with disease modifying therapy (hydroxycarbamide or transfusion) do have an improved survival compared with three decades ago. But this improvement in median life expectancy hides the underlying high rates of early death, and patients with complications such as pulmonary hypertension, renal failure or neurological disease are likely to die in the 20s or 30s as summarised above.

Chronic morbidity: Severe SCD is associated with a very significant rate of morbidity and mortality. The toll of SCD on the patient is considerable and includes: Years of pain and suffering; Loss of function of main organs (brain, lungs, liver, kidneys, heart, spleen); Difficulty in maintaining social functioning; Difficulty in maintaining employment and most SCD patients do not enter the workforce.

Significant neurological vascular events (i.e. stroke) are common in SCD and are a devastating complication. Despite long term transfusion therapy 10-22% of patients who have experienced a stroke will have a subsequent stroke event. Successful

HSCT will prevent recurrent stroke i.e. HSCT has a major impact on mortality, and also on morbidity.

Current therapy

Current therapies include hydroxycarbamide and blood transfusion. Hydroxycarbamide is the only licensed medication and should be offered to all children with sickle cell anaemia (HbSS), with the aim of reducing acute pain episodes and other acute complications. It should be offered to all adults with repeated acute pain crises, episodes of acute chest syndrome, or severe anaemia.

It can be highly effective, but some individuals will continue to have acute complications despite its use. It is also associated with side effects including myelosuppression, which may limit the dosages used. Blood transfusion is offered to children who have been identified as having an increased stroke risk with raised trans-cranial Doppler blood flow. In adults and children, it is standard care for secondary stroke prevention and is also used in individuals who have persistent pain episodes despite treatment with hydroxycarbamide. Chronic blood transfusion is associated with side effects including iron overload and obtaining repeated venous access can be challenging and distressing. Some patients develop red cell allo-antibodies and/or delayed haemolytic transfusion reactions rendering them difficult to transfuse and precluding the use of regular blood transfusion.

A small population of patients do not respond to hydroxycarbamide and are difficult to transfuse: for these patients we have no alternative treatments. These patients face a life of intermittent severe pain, frequent hospital admissions and an elevated risk of early death in their 20's to 40's. It is no surprise therefore that health related quality of life in adults with sickle cell disease is significantly worse than the general population, with scores that are in keeping with those seen in patients on long term haemodialysis (McClish et al 2005 Health Quality Life Outcomes).

Of the approximate 12-14,000 patients with SCD in the UK, approximately 7-8000 are adults. 10-15% have severe disease with recurrent pain events, recurrent acute complication or severe chronic complications (e.g. stroke). Estimates would indicate that between 128-138 patients may be both eligible and willing to proceed to HSCT at present, including a back-log of patients who are awaiting this treatment. Of these

only around 30% would have a fully matched sibling donor (i.e. 30-40 patients). In view of the back log of eligible patients currently awaiting HSCT we would expect this number to be reduced in subsequent years.

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

- Five uncontrolled studies were included in this evidence review, each including at least 20 adults with SCD. Four of the included studies reported outcomes for adults (Ozdogu et al 2018; Allen et al 2017; Fitzhugh et al 2017; Hsieh et al 2014); one reported outcome for a mixed population of children and adults which included some outcomes reported separately for adult patients aged at least 16 years (Gluckman et al 2017). Sample sizes (for adults only) ranged from 20 to 154. Median follow-up (where reported) ranged from 3.17 to 4.3 years; one study (Ozdogu et al 2018) reported mean follow up as 13.8 months, with most outcomes reported at one year.
- There was some overlap in reporting of results by three of the included studies: Allen et al (2017) reported results for patients enrolled in three different trials, one of which was also reported by Fitzhugh et al (2017) and another of which was reported by Hsieh et al (2014).
- The studies involved different donor types: two studies involved only HLA matched sibling donors (Gluckman et al 2017; Hsieh et al 2014); one study involved only HLA-matched related donors (Ozdogu et al 2018); one study involved only haploidentical donors (Fitzhugh et al 2017), and one study included both HLA-matched sibling donors and haploidentical donors (Allen et al 2017).
- The study by Gluckman et al (2017) included patients who received HSCT using either PB or BM cells and either non-myeloablative (nMAC) or myeloablative (MAC) conditioning regimens. The other four studies included only patients who received HSCT using PB stem cells and nMAC regimens.
- No studies compared HSCT with alternative treatment strategies.

Clinical effectiveness

- Overall survival (4 studies, total n=227[1], range n=20 to n=154). This ranged from 81% (95%CI 74% to 88%) five-year probability of overall survival after median follow-up of 48.0 months (range 2.18 to 305.9) (Gluckman et al 2017) to 100% at one year follow-up (Ozdogu et al 2018), both studies involving HLA-identical donors. In the other two studies, overall survival was 87% after median follow-up 3.17 years in a study using haploidentical donors (Fitzhugh et al 2017), and 97% after median follow-up 3.4 years (range 1 to 8.6)[2] in a study of HLA-identical donors (Hsieh et al 2014); neither or these studies reported 95% confidence intervals.
- Event-free survival (EFS)[3] (1 study, n=154). Five-year probability of EFS was 81% (95%CI 74% to 87%) at median follow-up of four years in a study using HLA-identical donors (Gluckman et al 2017).
- Disease-free survival (DFS) (3 studies, total n=73, sample sizes n=20, n=23, n=30). DFS ranged from between 35% and 50%[4] in a study of HSCT using haploidentical related donors (median follow-up 3.17 years) (n=23) (Fitzhugh et al 2017) to 87% in a study of HSCT using HLA-identical related donors (median follow-up of 3.4 years) (n=30) (Hsieh et al 2014). A third study (n=20), using HLA-identical donors, reported DFS of 100% at one year post-transplant (Ozdogu et al 2018).
- Non-relapse mortality (NRM) (2 studies, total n=50, sample sizes n=20, n=30). One study reported that no patients had died one year post-HSCT (Ozdogu et al 2018); the second study reported that no patients had died without relapse or recurrence after median follow-up of 3.4 years (Hsieh et al 2014). Both studies involved HLA-identical donors.

.[1] Including three patients who did not have SCD but who were included in the study populations of Fitzhugh et al (2017) and Hsieh et al (2014) and for whom results were not reported separately

[2] Inconsistent reporting of median follow-up as 3.4 years (range 1.0 to 8.6) or 3.6 years (range 1.0 to 8.4); for the purposes of this review, the first set of figures (reported in both published abstract and main text of paper) is used for the remainder of the results (section 4)

[3] Defined by Gluckman et al (2017) as the probability of being alive with sustained donor cell engraftment

[4] Disease-free survival for total study population was 35%; disease-free survival for cohort 3 (with highest does of post-transplant cyclophosphamide, 100mg/kg) was 50%

- Engraftment (4 studies, total n=73[5], range n=20 to n=61). The proportion of patients with sustained engraftment ranged from 77% in a study of HSCT from mixed-type donors[6] (median follow-up 4.3 years) (Allen et al 2017) to 87% in a study using HLA-identical sibling donors (which included 1 adult without SCD) at median follow-up 3.4 years (Hsieh et al 2014). A third study using haploidentical donors reported that 70% achieved engraftment by 100 days post-transplantation (Fitzhugh et al 2017). Median time to engraftment (where reported by one study) was 14 days (Allen et al 2017).
- Donor chimerism (3 studies, total n=73, sample sizes n=20, n=23, n=30). Mean donor chimerism at one year post-transplant ranged from 83% (Hsieh et al 2014) to 100% (Ozdogu et al 2018); both studies used HLA-identical donors. Mean donor myeloid-cell chimerism ranged from 84.8% (±SE 8.8) in a study using haploidentical donors (Fitzhugh et al 2017) to 86% (95%CI 70% to 100%) in a study using HLA-identical donors (Hsieh et al 2014). Mean donor T-cell chimerism (1 study) was 48% (95% CI 34% to 62%) at median follow-up of 3.4 years after HSCT using HLA-identical donors (Hsieh et al 2014).
- Quality of life (1 study, n=20). One study (Ozdogu et al 2018) measured quality of life before and one year after HSCT using HLA-identical donors via the short form SF-36 and reported a statistically significant improvement in post-transplant scores at one year in two SF-36 domains: health general (before 21.0 ± SD 22.3, after 71.9 ± SD 21.7; p=0.005) and bodily pain (before 30.6 ± SD 27.2, after 93.9 ± SD14.5; p=0.004). The clinical significance of these changes was unclear. For another five (of eight) SF-36 domains for which results were reported, there were improvements in the post-HSCT scores but the difference was not statistically significant. No results were reported for the SF-36 physical functioning domain.

[5] Allen et al (2017) (n=61) reported results for adults with SCD from the same study populations as Fitzhugh et al (2017) (n=21 adults with SCD, n=2 without SCD) and Hsieh et al (2014)(n=29 adults with SCD, n=1 without SCD) together with results from a third NIH trial (n not reported separately). Allen et al had an earlier study endpoint (31 March 2015) than Fitzhugh et al (2017) and Hsieh et al (2014) which may account for the smaller sample of SCD adults with haploidentical donors in the Allen et al study (n=19 vs n=21)

[6] HLA-identical or HLA-haploidentical

- Immunosuppression (2 studies, total n=50, sample sizes n=20, n=30). In one study, 60% of patients had stopped taking immunosuppressants at one year post-HSCT (Ozdogu et al 2018); in the second study, 50% of patients stopped taking immunosuppressants after median follow-up of 3.4 years, and median duration of immunosuppression medication after HSCT was 2.1 years (Hsieh et al 2014). Both studies involved HLA-identical donors.
- Hospitalisation (2 studies, total n=50, sample sizes n=20, n=30). In one study, 90% of patients had at least one hospital admission per year pre-HSCT; the proportions of patients with at least one hospital admission post-HSCT, were: 30% (of n=20) at 100 days, 20% (of n=16) at 180 days and 5% (of n=12) at one year. No p values were reported (Ozdogu et al 2018). In the second study (Hsieh et al 2014), mean annual hospitalisation rate[7] (number of hospitalisations per patient per year) for the year pre-transplant was 3.23[8] (95%CI 1.83 to 4.63), and for the first, second and third years post-transplant: 0.63 (95%CI 0.26 to 1.01), 0.19 (95%CI 0 to 0.45), and 0.11 (95%CI 0.04 to 0.19) respectively. Both studies involved HLA-identical donors.
- Blood transfusion requirement (2 studies, total n=91, sample sizes n=30, n=61). In one study involving HLA-identical donors, 53% (n=16/30) patients received simple/exchange red blood cell (RBC) transfusions pre-HSCT (number/frequency not stated); post-HSCT, 3% (n=1) needed transfusions for up to 1.5 years; median follow-up of 3.4 years (Hsieh et al 2014). The second study (which included both HLA-matched sibling donors and haploidentical donors) did not report blood transfusion requirements in comparable units pre- and post-HSCT. Pre-HSCT, 46% of patients required more than 50 units of transfused RBCs, 34% required 11 to 50 units, and 11% required one to ten units[9]; post-HSCT, median time to transfusion independence was 19 days (Allen et al 2017).

[7] Data for mean annual hospitalisation rate were reported only in published abstract. Full paper included chart showing median hospitalisation rate per patient per year but the data were not reported separately
[8] All hospitalisations in year before transplantation were for SCD-related complications (7 patients had ≥ 5 hospitalisations; 13 patients had between 1 and 4 hospitalisations)
[9] Transfusion requirement not known in a further 8% of patients

- Narcotic use (2 studies, total n=50, sample sizes n=20, n=30). In one study, 85% of patients were using narcotics[10] pre-HSCT; after HSCT, at 100 days, 180 days, and one year, the proportions of patients using narcotics were: 10% (n=2 of 20); 5% (n=1 of 16) and 0% (n=0 of 12) respectively (Ozdogu et al 2018). In the second study, 37% of patients were on long-term narcotics[11] at baseline (mean narcotics use per week at time of transplantation 639 mg (95%CI 220-1058)) (Hsieh et al 2014). Six months after HSCT, this had reduced (to 140 mg (95%CI 56-225)). Six patients (20% of total study population, 55% of those on long-term narcotics at baseline) were successfully weaned from long-term narcotics after transplant (median follow up 3.4 years). Neither study reported any p values. Both studies involved HLA-identical donors.

Safety

- Graft failure and/or rejection[12] (4 studies, total n=73[13], range n=20 to n=61). In one study, which included both HLA-matched sibling donors and haploidentical donors, graft failure occurred in 23% of patients (engraftment/primary graft failure in 7% (n=4/61), and secondary graft rejection in 16% (n=10/61). In a second study involving haploidentical donors, graft failure occurred in 65% (n=15/23) (including two patients without SCD) (primary graft failure 30% (n=7/23), secondary graft failure 35% (n=8/23)) (Fitzhugh et al 2017). In a third study involving HLA-identical donors, 13% (n=4/30) (including one patient without SCD) had temporary donor engraftment for one to three months post-HSCT, then (secondary) graft failure and subsequent autologous recovery (Hsieh et al 2014). In the fourth

[10] Not defined
[11] Taking long-and short-acting narcotics for at least three months
[12] Use of the terms 'engraftment failure', 'graft failure', and 'graft rejection' varied between studies. In this review, the term 'graft failure' refers to all cases of graft failure/rejection, the term 'engraftment/primary graft failure' is used to mean the proportion of patients in whom engraftment did not occur, and the term 'secondary graft failure/rejection' are used to mean the proportion of patients in whom primary engraftment occurred but the graft subsequently failed or was rejected.
[13] Allen et al (2017) (n=61) reported results for adults with SCD from the same study populations as Fitzhugh et al (2017) (n=21 adults with SCD, n=2 without SCD) and Hsieh et al (2014) (n=29 adults with SCD, n=1 without SCD) together with results from a third NIH trial (n not reported separately). Allen et al had an earlier study endpoint (31 March 2015) than Fitzhugh et al (2017) and Hsieh et al (2014) which may account for the smaller sample of SCD adults with haploidentical donors in the Allen et al study (n=19 vs n=21)

study involving HLA-identical donors, no patients (n=0/20) had (secondary) graft failure/rejection at one and two years post-HSCT (Ozdogu et al 2018). Median time to secondary graft failure/rejection (where reported) ranged from a median of 93.5 to 108.5 days.

- Graft versus host disease (GvHD) (4 studies, total n=237, range n=20 to n=154). Cumulative incidence of acute GvHD (2 studies) was 0% in a study using HLA-identical donors (Hsieh et al 2014) to 9% in a study using haploidentical donors (Fitzhugh et al 2017) (median follow-up 3.17 to 3.4 years). In a third study involving HLA-identical donors, risk of acute GvHD increased with age across the total study population (n=846 children; n=154 adults) (hazard ratio 1.04 (95%CI 1.01 to 1.07), p=0.008) (Gluckman et al 2017). Cumulative incidence of chronic GvHD (3 studies, all involving HLA-identical donors) ranged from 0% (Ozdogu et al 2018; Hsieh et al 2014) to 19.6% (95%CI 13.3% to 26.8%) (Gluckman et al 2017). Five-year probability of GvHD-free survival in one study was 77% (95% CI not reported) (Gluckman et al 2017).
- Painful crisis (1 study, n=20) (Ozdogu et al 2018). Pre-HSCT, 90% of patients (all with HLA-identical donors) had painful crises (number/frequency not reported); post-HSCT (at 100 days, 180 days, and one year), no patients had painful crises. No p values were reported.
- Transplant-related infections (3 studies, total n=73, sample sizes n=20, n=23, n=30) (Ozdogu et al 2018; Fitzhugh et al 2017; Hsieh et al 2014). The proportion of patients who had specific infections diagnosed or suspected ranged from 27% (n=8/30) in a study using HLA-identical donors (Hsieh et al 2014) to 57% (n=13/23) in a study using haploidentical donors (Fitzhugh et al 2017). Infections were most commonly CMV-related and of varying severity.
- Transplant-related complications (not infections or changes in end-organ function) (4 studies, total n=134, range n=20 to n=61). The largest study, involving both HLA-matched sibling donors and haploidentical donors (Allen et al 2017), reported immunohaematological complications in 15% (n=9/61) patients after median follow-up 4.3 years; these were associated with significant clinical events in 8% (n=5) of cases; by the end of the study, 78%

(7 of the 9 patients) were still alive. Amongst the other three studies, one involving HLA-identical donors reported that 50% of patients (and 50% of donors) experienced side effects (including minor pain, headache, paraesthesia, fatigue) related to granulocyte-colony stimulating factor (G-CSF) and plasma apheresis, and 15% of patients had hyperlipidaemia (Ozdogu et al 2018). In the second study, complications occurred in 61% (n=14/23[14]), after HSCT using haploidentical donors (Fitzhugh et al 2017). In the third study, involving HLA-identical donors, all patients (n=30[15]) experienced at least one severe adverse event (SAE); a total of 38 SAEs were reported, of which 6 SAEs were infections[16] (Hsieh et al 2014). The most common SAEs in this study were classed as 'pain and related management' (e.g. arthralgias, myalgias, narcotics withdrawal)

- Changes in end-organ function (2 studies, total n=50, sample sizes n=20, n=30):
- hepatic function (2 studies, total n=50, range 20 to 30). In one study, 40% (n=8/20) patients had temporary rises in serum aminotransferase persisting for up to two months after HSCT (Ozdogu et al 2018). In the second study (Hsieh et al 2014), approximately two-thirds of patients had temporary variable increases in transaminases and alkaline phosphatase post-HSCT; 50% (n=15/30) patients had ferritin levels >1000ng/mL at baseline. Of these, nine had liver biopsy, and eight of these nine had histology available which showed varying levels of inflammation. No baseline measure was available for comparison. Both studies involved HLA-identical donors.
- renal function (1 study, n=30) (Hsieh et al 2014). Before HSCT, 13% (n=4) had sickle nephropathy (serum creatinine ≥ 1.3mg/dL); no worsening of a previously established decline in renal function was observed post-transplant.
- cardiopulmonary function (1 study, n=30) (Hsieh et al 2014). Before HSCT 43% (n=13) had tricuspid regurgitant velocity (TRV) >2.5 m/s. Mean TRV pre-transplant was 2.84m/s (95% CI 2.71 to 2.99); this reduced to 2.57m/s (95%

[14] Including two patients with β-thalassaemia and not SCD
[15] Including one patient with β-thalassaemia, not SCD
[16] Hsieh et al's (2014) reporting of SAEs included infections; the number/proportion of SAEs not involving infections were not separately reported

CI 2.44 to 2.69) one month after transplant (n not stated), to 2.43m/s (95% CI 2.12 to 2.70) at one year (n not stated) and 2.33m/s (95% CI 2.14 to 2.51) at three years (n not stated, p values not clearly stated). Before transplant, mean distance walked in six minutes was 455m (95% CI 244 to 665); at one year post-HSCT it was 504m (95% CI 206 to 801), and at three years it was 507m (95% CI 332 to 681) (p=0.41).

- CNS function (1 study, n=30) (Hsieh et al 2014). There were no cases of stroke or cerebral bleeding peri-transplant in the 30% (n=9) of patients who had a history of stroke or abnormal CNS vessels pre-transplant. Post-HSCT annual brain MRI scans were unchanged in patients with sustained engraftment; one patient who relapsed died from recurrent stroke. One patient with a history of infrequent complex partial seizures had two self-limited episodes within the first three months post-HSCT (median follow up 3.4 years).
- Large volume phlebotomy (one study, n=30) (Hsieh et al 2014). 43% required large volume phlebotomy post-transplant for the treatment of iron overload; of these, 23% (n=7) had completed phlebotomy and 20% (n=6) continued to undergo phlebotomy by the end of the study (median follow up 3.4 years). The study involved HLA-identical donors.

Cost-effectiveness

- No studies were identified reporting the cost-effectiveness of allogeneic HSCT in adults with SCD compared with alternative treatment strategies.

Subgroups

- There are some apparent differences in outcomes (e.g. survival and graft failure) reported for patients with different donor types but the findings are difficult to interpret because of significant confounding. One study (Allen et al 2017) published data on HSCT outcomes in adults with SCD according to donor type (HLA-identical vs haploidentical). Total graft failure (primary and secondary) rates were: 12% (n=5/42) vs 47% (n=9/19); engraftment (primary graft) failure rates were 0% (n=0/42) vs 21% (n=4/19); secondary graft rejection rates were 12% (n=5/42) vs 26% (n=5/19). Median follow-up was

around 4.3 years. No p values were reported. Reported characteristics of patients indicate that patients with haploidentical donors may have had higher morbidity at baseline than those with HLA-identical donors. Another study (Gluckman et al 2017) included adult SCD patients who had received HSCT using either PB stem cells (n=43, 28%) or BM stem cells (n=111, 72%) but results were not reported separately for these groups. None of the other included studies investigated whether the clinical effectiveness of HSCT varied for different subgroups of adults with SCD or with different approaches to HSCT.

Conclusions

- All the studies included in this review were uncontrolled and involved median follow-up of less than five years; three of the five studies included fewer than 30 adults with SCD. This limits the conclusions that can be drawn about the clinical effectiveness and safety of HSCT in adults with SCD, and about HSCT compared with other treatment approaches. Data reported by one retrospective study suggest that HSCT using HLA-identical donors may be associated with lower rates of graft failure than HSCT using haploidentical donors but these results may be affected by confounding.

8 Proposed Criteria for Commissioning

For patients with sickle cell disease, stem cell transplantation remains the only curative therapy. The evidence reviewed above indicates that stem cell transplantation is curative in a subgroup of patients. The patients most likely to benefit are those that have severe disease, have failed to respond to currently available treatment and who have no other therapeutic alternatives.

In addition to disease severity the success of stem cell transplantation depends on the donor type therefore only those patients with a fully matched sibling donor and meeting the indication for transplantation criteria will be routinely commissioned for HSCT.

Prior to proceeding the patient must be discussed and agreed in the national haemoglobinopathy MDT. After approval by the national MDT, the decision must be

ratified in the local transplant MDT after all pre-transplant fitness assessments have been completed to ensure the patient is fit enough to proceed to the transplant.

Indication for transplantation in terms of sickle cell disease

Patients who meet <u>any one</u> of the following criteria could be considered for HSCT.

1. Clinically significant neurologic vascular event or deficit lasting > 24 hrs and confirmed radiologically.
2. History of ≥2 acute chest syndrome despite optimum treatment with hydroxycarbamide (HC) or transfusion therapy
3. History of ≥3 severe pain crises or other acute complications per year despite the institution of supportive care measures (optimum treatment with HC or transfusion therapy). Other acute complications would include acute hepatopathy or splenic sequestration or acute priapism
4. Administration of regular transfusion therapy, either by simple transfusion or exchange transfusion with the aim to prevent severe sickle complications by maintaining a low HbS %. Severe sickle complications include a history or >/=2 chest syndromes, >/= 3 painful crisis per year, or severe recurrent priapism.
5. Patients assessed as requiring transfusion but with red cell allo-antibodies/very rare blood type, rendering it difficult to continue/commence chronic transfusion.
6. Patients requiring HC/transfusion for treatment of SCD complications who cannot tolerate either therapy due to significant adverse reactions.
7. Established and related end organ damage relating to sickle cell disease, including but not limited to progressive sickle neurovasculopathy and hepatopathy.

To determine fitness to proceed to HSCT, patients should have <u>all the following</u>:

1. Karnofsky score ≥60

2. Cardiac function: LVEF ≥45% or shortening fraction ≥25%.

   Note: For subjects who have history of iron overload or serum ferritin levels >1000 ng/mL, a cardiac MRI is required. Cardiac T2* <10 ms results in exclusion.

3. Lung Function: FEV_1, FVC and DLCO ≥50%

4. Renal function: EDTA GFR ≥40 ml/m^2/1.73m^2

5. At least one first degree relative willing to act as a donor and confirmed as fully matched sibling donor.

9 Proposed Patient Pathway

The patient pathway is described in detail in the service specifications:

- Haematopoietic stem cell transplantation (adult) https://www.england.nhs.uk/wp-content/uploads/2013/06/b04-haema-adult.pdf

The HSCT commissioning pathway commences with the decision to transplant and ends 100 days following the transplantation procedure. This pathway does not preclude shared-care arrangements for post-transplant follow-up between the transplant centre and local providers, where this has been agreed between providers.

Beyond 100 days, commissioning responsibility for haematology follow-up of adult patients will transfer to the patient's Clinical Commissioning Group.

Proposed pathway:

- Patients assessed as meeting criteria by physician with expertise in SCD
- Patients referred to transplant physician for evaluation and discussion of eligibility for transplant
- Patient discussed at National Haemoglobinopathy Panel and decision made whether patient can proceed or not proceed to transplant. MDT must consist of physicians experienced in the treatment of SCD and transplantation

- Patient admitted to agreed JACIE accredited transplant centre. Transplant centre must have access to experienced sickle team who are able to attend on site for joint review of patients.
- Patient discharged to transplant and sickle service for ongoing follow-up.

10 Proposed Governance Arrangements

The governance arrangements are described in detail in the HSCT service specifications for adults (B04/S/a).

All providers of HSCT must be Joint Accreditation Committee-ISCT & EBMT (JACIE) accredited.

NHSE will commission from combined specialised Haemoglobinopathy and HSCT centres, which must have the appropriate level of expertise, experience and infrastructure to deliver HSCT in this patient population. Decisions on patient treatment will be undertaken by the existing National Haemoglobinopathy Panel with clinical transplantation input, with commissioner oversight of the governance arrangements.

The National Haemoglobinopathy Panel will review the outcome of each case at bi-annual meetings, with commissioner involvement, and annually audit outcomes against this policy.

Bone marrow or peripheral blood stem cells may be used as donor stem cell sources. Use of umbilical cord cells is not recommended as a donor stem cell source.

11 Proposed Mechanism for Funding

Funding for stem cell transplantation is through the NHS England teams responsible for specialised commissioning. The funding arrangements are described in detail in the BMT service specifications for adults (B04/S/a) and children (B04/S/b) respectively.

12 Proposed Audit Requirements

Complete data must be submitted to the BSBMT registry for all transplants carried out by centres in England. This will enable better evaluation of clinical outcomes

broken down by patient and disease-related variables. All centres must undergo regular JACIE inspection. All centres must provide the data required for the BMT Quality Dashboard. Audit requirements are described in more detail in the BMT service specification.

Outcome data for allogeneic transplants for sickle cell disease must be separately identifiable within the BSBMT database, and included within the annual BSBMT report to commissioners, which is fed back to participating centres.

It is a requirement that a complete data set is submitted to the European Society for Blood and Marrow Transplantation's Registry (EBMT)

To ensure shared practice and expertise, all providers will participate in an 'all ages annual confidential audit meeting' where the outcomes of all transplanted patients are discussed.

13 Documents That Have Informed This Policy Proposition

This document updates and replaces
Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised (January 2015). Reference: NHS England B04/P/a
HSCT Service Specifications for adults, B04/S/a and children B04/S/b
Specialised Services for Haemoglobinopathy Care (All Ages) B08/S/a

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or not for routine commissioning.

15 References

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