MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
November 2019

Agenda Item No	
National Programme	Blood and Infection
Clinical Reference Group	BMT and Haemoglobinopathies CRGs
URN	1830

Title
Haematopoietic stem cell transplantation for sickle cell disease (adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
Routinely Commissioned The policy is routinely commissioned for treatment of patients with severe sickle cell disease with a related donor that is fully HLA matched to the recipient (sibling) However, at this time NHS England 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 (haploidentical). 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. 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.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report
2.	The Head of Acute Programmes confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

No	*Metric*	*Summary from evidence review*
1.	Survival	Overall survival is the proportion of participants alive at specified intervals. In the study of adults (aged ≥16 years, median age 19.3 years) with SCD (Gluckman et al 2017), the probability of overall survival at five years after HSCT was 81% (95%CI, 74%-88%). Median follow-up was 48.0 months (range 2.18-305.9) but the number of patients alive at different time points was not reported. The probability of overall survival at five years was 81%. A high overall survival rate is important to clinicians, patients and their

		families. However, this study does not demonstrate that overall survival is improved by the intervention. This uncontrolled retrospective review of international registry data included 154 adults (aged ≥16 years, median age 19.3 years) with SCD who received HSCT from HLA-identical sibling donors using myeloablative (n=113, 73%) or reduced intensity conditioning (n=40, 26%) regimens in the period 1989 to 2013. Median follow-up was 4 years although some patients were followed up for longer periods (of up to 25 years). The retrospective design introduces the possibility of selection bias. Heterogeneity amongst the study population, HSCT donor type and conditioning protocols limits generalisability of the study results. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	Painful crisis refers to the acute painful sickle cell episodes caused by blockage of the small blood vessels in patients with SCD, measured in terms of frequency of painful crises. In a study by Ozdogu et al (2018), pre-transplant, n=18 of 20 (90%) patients had at least two painful crises per year; post-transplant, the numbers (and %) of patients who had at least two painful crises were: n=0/20 (0%) at 100 days, n=0/16 (0%) at 180 days, and n=0/12 (0%) at 1 year, p values not reported. The proportion of patients who had at least two painful crises per year reduced from 90% pre-transplant to 0% post-transplant. The elimination of painful crises is important for clinicians, patients and their families because it also reduces the need for pain management and hospitalisation and improves quality of life. The study by Ozdogu et al 2018 was a small, uncontrolled retrospective study of 20 adult patients with SCD treated consecutively at one centre in Turkey. The patients were all of Eti-Turk origin which limits generalisability of its results. Follow-up for most outcomes, including hospitalisation, was short (one year or less). As the study does not include a comparator it is not possible to compare the outcomes for the study population with patients receiving alternative treatments.
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	

9.	Dependency on care giver / supporting independence	
10.	Safety	See below
11.	Delivery of intervention	

No	Metric	*Summary from evidence review*
1.	Event free survival	Event free survival refers to the time from transplant to graft failure, graft rejection or death from any cause. The outcome was defined by Gluckman et al (2017) as the probability of being alive with sustained donor cell engraftment. In a study of adults (aged ≥16 years, median age 19.3 years) with SCD (Gluckman et al 2017), the probability of event-free survival at five years was 81% (95%CI: 74%-87%). Median follow-up was 48.0 months (range 2.18-305.9) but the number of patients alive at different time points was not reported. Event free survival was 81% at five years after HSCT. A high event free survival rate is important to clinicians, patients and their families. However, this study does not demonstrate that event-free survival is improved by the intervention. These results should be treated with caution as stated in Table 1, no 1 (Gluckman 2017).
2.	Disease-free survival	Disease-free survival is the proportion of participants alive, without re-emergence of SCD, at specified intervals. In a study of HSCT in adults with SCD using haploidentical donors (Fitzhugh et al 2017), disease free survival was 35% for the total study population (n=23) and 50% for the cohort of patients (n=12) who received the highest dose of post-transplant cyclophosphamide (100 mg/kg) but it was not clear how patients were initially allocated to the different cyclophosphamide regimens; median follow-up was 3.17 years (range 0.67 - 6.16). In a second study of HSCT in adults with SCD using HLA-matched sibling donors (Hsieh et al 2017) (n=30), disease free survival was 87%; median follow-up was 3.4 years (range 1 - 8.6)[1]. Disease-free survival was 35% to 50% in the study involving haploidentical donors, and 87% in the study involving HLA-matched sibling donors. High rates of disease free survival are important to clinicians, patients and their families. However, these studies do not demonstrate that disease-free survival is

[1] Inconsistent reporting of median follow up in published study as 3.4 years (range 1.0 to 8.6) and 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 in this table

		improved by the intervention, nor that differences in outcome can be attributed to donor type. Both studies were small uncontrolled prospective studies of HSCT in adults with SCD and/or thalassaemia using non-myeloablative conditioning regimens. In Fitzhugh et al (2017), n=21 adults with SCD (of 23 patients enrolled in the study) received HSCT from haploidentical donors; in Hsieh et al (2014), n= 29 adults with SCD (of 30 enrolled) received HSCT from HLA-matched sibling donors. The median follow-up for both studies was less than 4 years. In both studies, results were not reported separately for the patients who did not have HbS but who had β-thalassaemia and may have a different risk profile and outcomes compared with SCD patients. Since neither study included a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.
3.	Non-relapse mortality	Non-relapse mortality is the time to death without relapse or recurrence. In the study by Hsieh et al (2017), no patients died without relapse or recurrence by the end of the study. Median follow-up was 3.4 years (range 1 - 8.6). Non-relapse mortality was very low (no cases were reported). A very low non-relapse mortality is important to clinicians, patients and their families. However, this study does not demonstrate that non-relapse mortality is improved by the intervention. This small uncontrolled prospective study included 30 adult patients with SCD and/or thalassaemia who received HSCT using a non-myeloablative conditioning regimen and HLA-matched sibling donors. One patient enrolled in the study had β-thalassaemia without SCD; results were not reported separately for this patient who may have a different risk profile and outcomes following HSCT compared with SCD patients. The median follow-up was less than 4 years. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.
4.	Engraftment	Engraftment occurs when the stem cells of the donor have been taken up by the patient's bone marrow and produce new blood and immune system cells. Engraftment outcomes include engraftment 100 days post-transplant (Fitzhugh et al 2017), graft maintained at study endpoint (Allen et al 2017), neutrophil engraftment at 30 days and mean time to neutrophil engraftment (defined as the first of three consecutive days on which the absolute neutrophil count exceeded 0.5×10^9 cells/L) (Ozdogu et al 2018 and Hsieh et al 2014). In a study by Fitzhugh et al (2017) using haploidentical donors, the engraftment (not further defined) before 100 days post-transplant was 70% in the total study population (n= 23), and

		83% for the cohort of patients (n=12) who had the highest dose of post-transplant cyclophosphamide (100 mg/kg). In a second study by Hsieh et al (2017) (n=30), the rate of sustained donor leukocyte engraftment[2] was 87% (median follow-up 3.4 (range 1 - 8.6)[97]). Engraftment rates were 70% to 83%, before 100 days post-transplant in one study, and 87% at follow-up (median 3.4 years, range 1-8.6) in a second study. Engraftment, particularly if sustained, is a positive outcome of HSCT implying that the patient is successfully producing new blood and immune cells. However, these studies do not demonstrate that differences in outcome can be attributed to donor type. These results should be treated with caution as stated in Table 2, no 2 (Fitzhugh 2017, Hsieh 2014).
5.	Graft failure or rejection	Graft failure[3] refers to a lack of initial engraftment of donor cells (primary graft failure) or loss of donor cells after initial engraftment (secondary graft failure). Graft rejection is a form of graft failure due to recipient immune response against donor immunohaematopoietic cells. In the study by Fitzhugh et al (2017), of HSCT involving haploidentical donors, n=15 of 23 (65%) adult patients (comprising n=21 with SCD, n=2 with β-thalassaemia) had graft failure; of these, n=7 (30%) had primary graft failure, and n=8 (35%) had secondary graft failure at a median time post-transplant of 108.5 days (range 63 days to 2.35 years). A total of n=6 (26%) rejected their grafts but it was not specified how this group related to those with graft failure. Graft rejection occurred in n=1, at 7 months, in the cohort receiving no post-transplant Cy; in n= 1, acutely, in the cohort receiving 50mg/kg Cy, and n= 4 in the cohort receiving 100mg/kg Cy, at a median of 73.5 days (range 63-90). In the study by Hsieh et al (2014), of HSCT involving HLA-matched sibling donors, 4 of 30 (13%) adult patients (comprising n=29 with SCD, n=1 with β-thalassaemia) had temporary donor engraftment for 1 to 3 months post-transplant, with subsequent graft rejection and autologous recovery with SCD.[4] Graft failure rates varied widely between these two studies of HSCT using non-myeloablative conditioning regimens (from 13% in a study using HLA-matched sibling donors to 65% in a study using haploidentical donors). A low rate of graft failure is important to clinicians, patients and their families. However, these studies do not demonstrate that differences in outcome can be attributed to donor type.

[2] Defined as full donor-type Hb on Hb electrophoresis

[3] The terms graft failure and graft rejection were not defined by included studies and appeared to be used interchangeably by some studies

[4] One of these patients died from intracranial bleeding associated with previous moyamoya disease after relapse of SCD

		These results should be treated with caution as stated in Table 2, no 2 (Fitzhugh 2017, Hsieh 2014).
6.	Donor chimerism	Chimerism relates to the presence of donor cells after transplantation. Full or complete chimerism refers to 100% (as defined by Fitzhugh et al 2017) or almost 100% donor cells. Mixed chimerism refers to a combination of patient and donor cells. Chimerism may also be reported by cell lineage e.g. for myeloid cells and for CD3 cells (which are T-cells). In the study by Fitzhugh et al (2017), mean donor myeloid chimerism ranged from 0% to 84.8% (±SE 8.8) at different timepoints amongst patients with initial engraftment post-transplant; mean CD3 chimerism ranged from 0% to 57.7% (±SE 14.2); no patients achieved complete (100%) donor chimerism by the study endpoint (median follow-up 3.17 years (range 0.67 to 6.16)). In the study by Hsieh et al (2014), 25 of 30 (83%) adult patients (n=29 with SCD, n=1 with β-thalassaemia) had full donor-type haemoglobin at one year post-transplant; by the study endpoint, mean donor myeloid-cell chimerism was 86% (95%CI 70% to 100%), mean T-cell chimerism was 48% (95% CI 34% to 62%); no patients reached 100% donor chimerism in both myeloid and T-cell compartments (median follow-up 3.4 years (range 1 to 8.6)). The proportions of patients achieving full and mixed donor chimerism post-transplant varied between studies and over time. Achieving stable donor chimerism (full or mixed) with absent or reduced clinical manifestations of SCD is important to clinicians, patients and their families. However, these studies do not demonstrate that differences in outcome can be attributed to donor type. These results should be treated with caution as stated in Table 2, no 2 (Fitzhugh 2017, Hsieh 2014).
7.	Graft versus host disease	In graft versus host disease (GvHD) the donated cells react against the patient's body which can lead to an immune response attack. Acute GvHD usually starts within 100 days of transplant and chronic GvHD usually starts 100 days or more after transplant. Acute GvDH is graded as I = mild; II = moderate; III = severe; and IV = very severe. Chronic GvHD is generally graded as mild, moderate or severe[5]. In the study by Gluckman et al (2017), the risk for acute GvHD[6] was higher with increasing age (hazard ratio (HR) 1.04; 95%CI 1.01-1.07, p=0.008); for every one year increment in age at HSCT, there was a 4% increase in HR for acute GvHD. This finding was based on the whole study population of 1000

[5] https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf

[6] Cumulative incidence of grade II-IV aGvHD reported for total population of children and adults as 14.8% (95%CI 12.6-17.1) but not separately for adults; it is unclear whether these statements regarding increasing risk for aGvHD with age refer to all grades of aGvHD or only grades II-IV

		patients of all ages of whom 154 were aged ≥16 years. The cumulative incidence of cGvHD was about 20% (estimated from published graph; data not reported separately). Five-year probability of GvHD-free survival[7] for adult patients aged ≥16 years was 77% (no 95%CI reported). GvHD is an adverse outcome of HSCT and in severe cases can be life-threatening. The cumulative incidence of acute GvHD was not separately reported for adults with SCD but the risk appears to increase with age; around one-fifth of adult patients develop chronic GvHD. These results should be treated with caution as stated in Table 1, no 1 (Gluckman 2017).
8.	Quality of life	The SF-36 is a patient reported measure of health status which assesses Quality of Life (QoL) across eight domains, which are both physically and emotionally based. The eight domains are: physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; emotional well-being; social functioning; pain; general health. Scores are presented as a scale from 0 to 100. A high score indicates a more favourable health state. In one study (Ozdogu et al 2018) quality of life was measured before transplant and one year after transplant using the short form SF-36. There was a statistically significant improvement in the post-transplant scores at one year in two 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). For the other five domains for which results were reported there were improvements in the post-transplant scores but the difference between before and after transplant scores was not statistically significant. No results were reported for the physical functioning domain. There were statistically significant improvements in the SF-36 scores in two domains (health general and bodily pain); the clinical significance of this level of improvement is unclear. Improvements in quality of life are important for clinicians, patients and their families. However, this study does not demonstrate that quality of life is improved by the intervention. These results should be treated with caution as stated in Table 1, no 6 (Ozdogu 2018).
9.	Transfusion requirement (red blood cells)	Transfusion requirement refers to the frequency of red blood cell transfusions received by patients before and after transplantation.

[7] Defined as the probability of being alive without having experienced either grade III or grade IV aGVHD or extensive cGVHD

		In the study by Hsieh et al (2014), pre-transplant, n=16 (53%) patients had simple/exchange red blood cell transfusions (number/frequency not stated); post-transplant, one patient[8] (3%) needed transfusions for up to 1.5 years, achieving full donor red cell engraftment and transfusion free status at two years; no other patients were reported to have post-transplant transfusions. Median follow-up was 3.4 years (range 1 - 8.6[97]). In this study, the number of patients requiring red blood cell transfusions reduced after transplantation. A reduction in the requirement for red blood cell transfusions after transplantation is important for clinicians, patients and their families. These results should be treated with caution as stated in Table 2, no 3 (Hsieh 2014).
10.	Narcotic use	Narcotic use refers to the use of, or need for, narcotic drugs expressed as numbers of patients on long-term narcotics (defined by Hsieh et al 2014 as taking long-and short-acting narcotic drugs for at least three months) or mg intravenous morphine-equivalent dose per week. In the study by Hsieh et al (2014), n=11 of 30 (37%) patients were on long-term narcotics at baseline; mean narcotics use per week at time of transplant was 639 mg (95%CI 220 -1058), and six months after transplant was 140 mg (95%CI 56-225, no p values reported). Six patients (55% of those on long-term narcotics at baseline) were successfully weaned from long-term narcotics use after transplant (median follow up 3.4 years (range 1- 8.6)[97]). More than half of patients on long-term narcotics at baseline were weaned off long-term narcotics after receiving HSCT; there was a reduction in mean narcotics use per week after transplant but this was not statistically significant. Long-term narcotics use may be associated with significant adverse effects. A reduction in narcotics use, a proxy indicator of pain, is important for clinicians, patients and their families. These results should be treated with caution as stated in Table 2, no 3 (Hsieh 2014).
11.	Hospitalisation	Hospitalisation refers to the number or rate of hospital admissions per patient per year. In the study by Hsieh et al (2014), the mean annual hospitalisation rate[9] (reported as number of hospitalisations per

[8] Patient had detectable anti-Jka antibody to donor red blood cells pre-transplant

[9] Data for mean annual hospitalisation rate were reported only in published abstract. Full paper included chart showing median hospitalisation rate per patient per year; data for median hospitalisation rates were not reported separately

		patient per year) for the year pre-transplant was 3.23[10] (95%CI 1.83-4.63). Post-transplant (during the 1st year, 2nd year, and 3rd year), the mean annual hospitalisation rates were: 0.63 (95%CI 0.26-1.01), 0.19 (95%CI 0-0.45), and 0.11 (95%CI 0.04-0.19) respectively. The mean annual hospitalisation rate reduced after transplant for ≥3 years of follow-up. Reduced hospitalisation rates are important for clinicians, patients and their families. These results should be treated with caution as stated in Table 2, no 3 (Hsieh 2014).
12.	Immunosuppression	Immunosuppression refers to the use of immunosuppressant drugs following transplant. Cessation of immunosuppressant drugs (expressed as numbers and/or percentages of patients for whom this occurs) is a proxy indicator of immunological recovery. In the study by Fitzhugh et al (2017), involving haploidentical donors, all engrafted patients were still receiving immunosuppression at the study endpoint (median follow-up 3.17 years (range 0.67 to 6.16)). In the study by Hsieh et al (2014), involving HLA-matched sibling donors, median duration of immunosuppression post-transplant was 2.1 years (range 1.0-8.4); n=15 patients (50%) continued without taking immunosuppression medication[11] (median follow up 3.4 years (range 1 - 8.6)[97]). The proportion of patients who stopped taking immunosuppressants varied from 0% (in the study using haploidentical donors) to 50% (in the study using HLA-matched sibling donors). Cessation of immunosuppression via immunosuppressant drugs is a proxy indicator of immunological recovery post-transplant which is important for clinicians, patients and their families. However, these studies do not demonstrate that differences in outcome can be attributed to donor type. These results should be treated with caution as stated in Table 2, no 2 (Fitzhugh 2017, Hsieh 2014).
13.	Transplant-related infection	Post-transplant infection relates to the infections experienced by patients after transplantation. In the study by Fitzhugh et al (2017), n=15 (65%) patients had bacteraemia which responded to antibiotics and n=13 (57%) patients had specific infections diagnosed, most commonly CMV reactivation, CMV colitis, chronic EBV viraemia, and (presumed)

[10] All hospitalisations in year before transplantation were for SCD-related complications (7 patients had ≥ 5 hospitalisations; 13 patients had between 1 and 4 hospitalisations)

[11] Allowed one year after HSCT if donor CD3 chimerism more than 50%; one patient discontinued immunosuppression treatment independently despite having lymphoid chimerism of less than 50%

		fungal pulmonary nodules (each of these occurring in three or more patients). In Hsieh et al (2014), n=8 (27%) patients had specific infections diagnosed; the study also reported serious adverse events (SAEs) which included infections in n=6 (20%) patients, most commonly Clostridium difficile (n=2). The proportion of patients experiencing transplant-related infections varied between studies. Infections after transplantation can be life threatening. No grading system was used to specify the seriousness of the infections reported, other than the term 'serious adverse events' used by Hsieh et al (2014), so the clinical meaningfulness of the results is unclear. However, these studies do not demonstrate that differences in outcome can be attributed to donor type. These results should be treated with caution as stated in Table 2, no 2 (Fitzhugh 2017, Hsieh 2014).
14.	Transplant-related complications (non-infectious)	Transplant-related complications refer to adverse events which are related to the transplantation procedure, excluding infections (reported elsewhere). In the study by Fitzhugh et al (2017), n=7/23 (30%) patients experienced severe adverse events possibly or definitely associated with sirolimus, most commonly bone or joint pain and/or swelling, and nausea and/or abdominal pain; n=3/23 (13%) had other possible sirolimus-associated complications not classed as severe; n=4/23 (17%) patients had other complications unrelated to sirolimus, which were cardiac arrhythmias (n=2) and high grade myelodysplastic syndrome with fibrosis (n=2, both of whom died as a result of associated complications). In Hsieh et al 2014, 38 serious adverse events (SAEs) (including 6 SAEs which were infections), occurred in n=30 (100%) of the study population; 21 of these SAEs occurred in five patients. The most common SAEs were 'pain and related management' (n=15 SAEs) e.g. arthralgias, myalgias, narcotics withdrawal. The proportion of patients experiencing transplant-related complications varied between the two studies; in one study, 30% patients experienced severe adverse events possibly or definitely related to sirolimus; in the second study, all patients suffered one or more SAEs (including infections). Adverse events after transplantation can be life threatening so are important to clinicians, patients and their families. However, these studies do not demonstrate that differences in outcome can be attributed to donor type. These results should be treated with caution as stated in Table 2, no 2 (Fitzhugh 2017, Hsieh 2014).

15.	Changes in end organ function - renal	Nephropathy associated with sickle cell disease causes kidney (renal) complications as a result of sickling of red blood cells in the small blood vessels. In Hsieh et al (2014), n=4 (13%) patients had sickle nephropathy pre-transplant; no worsening of the previously established decline in renal function was observed in these patients post-transplant. No worsening in the decline in renal function associated with nephropathy after transplantation is important for clinicians, patients and their families. These results should be treated with caution as stated in Table 2, no 3 (Hsieh 2014).
16.	Changes in end organ function - cardiopulmonary	Measures used to assess cardiopulmonary function, specifically the risk of pulmonary hypertension which is a known complication in patients with sickle cell disease, include tricuspid regurgitant velocity (TRV) and the six-minute walk (6MW) test. TRV is measured via echocardiography and higher TRV indicates greater compromise of cardiopulmonary function. The 6MW test, usually performed on a treadmill, measures the distance in metres that the patient can walk in six minutes. In Hsieh et al 2014, at baseline, n=13/30 (43%) patients had TRV greater than 2.5m/s; mean TRV pre-transplant was 2.84 m/s (95%CI 2.71-2.99); mean TRV post-transplant was 2.57 m/s(95%CI 2.44 -2.69) at one month (n not stated), 2.43 m/s (95%CI 2.12-2.70) at one year (n not stated), 2.33 m/s (95%CI 2.14-2.51) at three years (n not stated), $p = 0.01$ for TRV 2.6 - 2.9m/s, $p < 0.001$ for TRV ≥ 3m/s. The mean 6MW test pre-transplant was 455m (95%CI 244 - 665) and post-transplant was 504m (95%CI 206 - 801) at one year, and 507m (95%CI 332 - 681) at three years, $p = 0.41$ (number of patients tested not reported). Changes in cardiopulmonary function after transplantation are important for clinicians, patients and their families. Statistically significant improvements were reported in TRV but not in the 6MWD test after transplantation; the clinical significance of these changes was not reported. These results should be treated with caution as stated in Table 2, no 3 (Hsieh 2014).
17.	Changes in end organ function – central nervous system	Complications of SCD include stroke, cerebral haemorrhage and epilepsy. Hsieh et al 2014 reported no cases of stroke or cerebral bleeding peri-transplant in nine patients with a history of stroke or abnormal CNS vessels pre-transplant. Subsequent post-transplant annual brain MRI scans were carried out in an unreported number of participants. MRI results 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 2 self-limited episodes at 2 and 3 months post-transplant. The prevention of strokes and seizures is important for clinicians, patients and their families. These results should be treated with caution as stated in Table 2, no 3 (Hsieh 2014).
18.	Changes in end organ function – hepatic	Damage to the liver can lead to increases in blood levels of enzymes such as transaminases and alkaline phosphatase. Liver biopsy can indicate changes in the structure of liver tissue. In Hsieh et al 2014, approximately two-thirds (n not stated) of 30 patients who received HSCT had variable increases in transaminases and alkaline phosphatase post-transplant; these parameters gradually improved with no specific treatment. Fifteen participants had ferritin levels >1000ng/mL at baseline. Of these, 9 had liver biopsy, and 8 of these 9 had histology available which showed varying levels of inflammation. No baseline measure was available for comparison. Changes in liver function after transplantation would be important for clinicians, patients and their families if they were related to changes in symptoms, quality of life or survival. It is unclear whether the changes reported by Hsieh et al 2014 were the result of the transplants, and what effect they had on patients. These results should be treated with caution as stated in Table 2, no 3 (Hsieh 2014).
19.	Large volume phlebotomy for iron overload	Large volume phlebotomy is the treatment for iron overload which is a complication of HSCT. In Hsieh et al 2014, n=13/30 (43%) patients required large volume phlebotomy for iron overload post-transplantation; of these, n=7 (23%) patients had completed phlebotomy and n=6 (20%) continued to undergo phlebotomy by the study endpoint (median follow up 3.4 years (range 1 - 8.6)[97]. Large volume phlebotomy is a proxy indicator for iron overload which is a complication of HSCT and is therefore important for clinicians, patients and their families. These results should be treated with caution as stated in Table 2, no 3 (Hsieh 2014).

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
Select appropriate option: 1) The proposal received the full support of the Blood and Infection PoC Board on the16th October 2019