NHS England

Evidence review: Haematopoietic stem cell transplantation for sickle cell disease (adults)

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Contents

1 Introduction

Introduction

- Sickle cell disease (SCD) is an inherited abnormality of haemoglobin resulting in recurrent severe pain crises and dysfunction of virtually every organ system in the body, ultimately causing premature death (Oringanje 2016).

- The objective of this review is to investigate the clinical effectiveness, cost effectiveness and safety profile of haematopoietic stem cell transplant (HSCT) in adults with SCD.

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- NICE clinical guidelines (CG143)[1] and quality standards (QS58)[2] refer to the management of SCD acute painful episodes in hospital. No NICE guidance was identified on HSCT for sickle cell disease.

The indication and epidemiology

- SCD is a group of disorders which occur when the variant haemoglobin S (HbS) gene is inherited from both parents (HbSS) (Serjeant 2001), or when HbS is co-inherited with variant haemoglobin (eg HbSC). The disease is characterised by recurrent acute pain crises and severe chronic health issues affecting neurological, cardiorespiratory, hepatic and renal systems.

- 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).

- Life expectancy for people with SCD is shorter than that for the general UK population. NHS England estimates life expectancy for people with SCD to be greater than 50 years in England (NHS England 2013); recent data from the UK has shown median survival of over 65 years (Gardner 2016).

- In addition to poor life expectancy, many patients continue to suffer health problems despite treatment. Societal and caregiver burden is high and significant health care costs are accrued by the NHS. Quality of Life (QoL) is impaired, impacting adversely on educational, employment and social outcomes which worsen with age.

[1] https://www.nice.org.uk/guidance/cg143
[2] https://www.nice.org.uk/guidance/qs58

Standard treatment and pathway of care

- The mainstay of treatment is supportive including infection prophylaxis with penicillin, vaccination and pain management, which have improved overall care but not impacted on morbidity.

- Only two disease modifying therapies are available: hydroxycarbamide (HC) (also known as hydroxyurea) and chronic blood transfusion therapy. Neither of these treatments are curative.

The intervention (and licensed indication)

- Haematopoietic stem cell transplantation (HSCT), also referred to as haemopoietic progenitor cell transplantation (HPC), involves replacement of the patient's stem cells with healthy donor cells; patients receive conditioning chemotherapy (which may be either myeloablative (MAC) or non-myelablative (nMAC), also referred to as reduced intensity conditioning (RIC)) followed by an infusion of stem cells (the transplant) from the donor.

- Sources of stem cells include bone marrow (BM) (bone marrow transplantation (BMT)) and peripheral blood (PB) (peripheral blood cell transplantation (PBSCT)). Most HSCTs involve allogeneic transplant (allo-HSCT), where the individual receives stem cells from another person, related or unrelated.

- The donor would ideally be a relative with an immunologic match (human leucocyte antigen (HLA) type match)[3] to the transplant recipient; other donor options include a matched unrelated donor or a haploidentical[4] related or unrelated donor.

- After the infusion of stem cells the patient is monitored in hospital whilst awaiting blood count recovery after the transplant. Patients can then be discharged home and will continue to be monitored in haematology outpatient departments. Ultimately the production of abnormal sickle red blood cells is replaced by the production of normal red cells which cures the SCD. Patients are discharged on immunosuppressive medication and remain on this for at least one year.

Rationale for use

- HSCT is considered to be the only curative option currently available for patients with SCD. A successful transplant would be expected to reduce chronic complications of SCD such as painful crisis and transfusion requirement, to reduce hospital admissions for SCD and improve quality of life.

- Whilst HSCT is established and available for children in this country, adults have not routinely been offered HSCT due to concerns about morbidity and mortality of HSCT in the context of accumulated comorbidities with older age.

- The development of reduced intensity conditioning protocols, which avoid the toxicities

[3] The definition of 'HLA matching' depends on the level of resolution and on which HLA loci are tested; the gold standard is high resolution typing at the HLA-A, -B, -C, -DRB1, and -DQB1 loci (10/10 match) (Tiercy, 2016).

[4] Donor and recipient HLA not fully matched (ie less than 10/10 match)

associated with myeloablative regimens (eg infertility and gonadal failure, chronic graft versus host disease (GvHD)[5]), provide an opportunity to offer HSCT as a curative option for adults with SCD (NHS England 2018).

2 Summary of results

- 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 outcomes 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[6], 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)[7] in a study of HLA-identical donors (Hsieh et al 2014); neither or these studies reported 95% confidence intervals.

- Event-free survival (EFS)[8] (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).

[5] An immune reaction of donor cells against recipient tissues and a potential for secondary malignancies
[6] 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
[7] 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)
[8] Defined by Gluckman et al (2017) as the probability of being alive with sustained donor cell engraftment

- Disease-free survival (DFS) (3 studies, total n=73, sample sizes n=20, n=23, n=30). DFS ranged from between 35% and 50%[9] 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.

- Engraftment (4 studies, total n=73[10], 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[11] (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.

- 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

[9] 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%

[10] 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)

[11] HLA-identical or HLA-haploidentical

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[12] (number of hospitalisations per patient per year) for the year pre-transplant was 3.23[13] (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[14]; post-HSCT, median time to transfusion independence was 19 days (Allen et al 2017).

- Narcotic use (2 studies, total n=50, sample sizes n=20, n=30). In one study, 85% of patients were using narcotics[15] 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[16] 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[17] (4 studies, total n=73[18], range n=20 to n=61). In one study, which included both HLA-matched sibling donors and haploidentical donors, graft failure

[12] 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

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

[14] Transfusion requirement not known in a further 8% of patients

[15] Not defined

[16] Taking long-and short-acting narcotics for at least three months

[17] 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.

[18] 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

occurred in 23% of patients (engraftment/primary graft failure in 7% (n=4/61), and secondary graft rejection[19] 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 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[20] 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[21] ranged from 27% (n=8/30) in a study using HLA-identical donors (Hsieh et al 2014)[22] 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,

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)

[19] Defined by Allen et al (2017) as the date on which chimerism studies showed no detectable donor CD3 or myeloid cells

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

[21] As opposed to bacteraemia or febrile neutropenia with no diagnosed/suspected specific infection

[22] Six infections were recorded as serious adverse events (SAEs)

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[23]), after HSCT using haploidentical donors (Fitzhugh et al 2017). In the third study, involving HLA-identical donors, all patients (n=30[24]) experienced at least one severe adverse event (SAE); a total of 38 SAEs were reported, of which 6 SAEs were infections[25] (Hsieh et al 2014). The most common SAEs in this study were classed as 'pain and related management' (eg 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% 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.

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

Subgroups
There are some apparent differences in outcomes (eg 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 of 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.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: Medline, Embase, and Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1st January 2008 and 16th August 2018.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in the review.
- In the absence of any controlled studies, only uncontrolled studies with a sample size of 20 or more adults with SCD undergoing HSCT were included. A further four studies, each involving between five and 19 adults with SCD, were excluded from the review by agreement with the NHS England Clinical Effectiveness Team, together with eight studies each with fewer than five adult SCD participants (five of these studies included only one adult with SCD).

- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).

- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4 Results

This evidence review identified five uncontrolled studies of HSCT in 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) and one reported outcomes 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). The range of sample sizes (for adults only, lowest age where defined ranged from 16 to 20 years) was from 20 to 154. The median follow-up (reported by four studies) 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. Three studies (Ozdogu et al 2018; Gluckman et al 2017; Allen et al 2017) were based on retrospective data and two (Fitzhugh et al 2017; Hsieh et al 2014) were prospective studies.

The included studies involved different approaches to HSCT (for example, in terms of stem cell type, donor type and conditioning regimen). However, in accordance with the PICO and NHS England evidence review methodology, the results have not been reported separately for each of the different HSCT approaches used.

Four studies investigated adults with SCD who received HSCT using PB stem cells and non-myeloablative conditioning (nMAC) regimens; the fifth study (Gluckman et al 2017) included adults with SCD who received HSCT using either PB or BM cells and either nMAC or MAC regimens. Three studies involved only HLA-identical donors (sibling or otherwise related) (Gluckman et al 2017; Hsieh et al 2014; Ozdogu et al 2018), one study involved only haploidentical donors (Fitzhugh et al 2017), and one study involved both HLA-matched sibling donors and haploidentical donors (Allen et al 2017).
There was some overlap in reporting of results by three of the included studies. Allen et al (2017) reported results for 61 patients enrolled across three different trials; one of these trials was reported by Fitzhugh et al (2017) (n=21 adults with SCD, n=2 without SCD), and another was reported by Hsieh et al (2014) (n=29 adults with SCD, n=1 without SCD). However, the extent of the overlap in reporting was not clear and there were differences across the three studies in the outcome measures reported and the study endpoints.
Full details of the study designs and outcomes are summarised in the evidence table in section 7. For the studies with overlapping populations (Allen et al 2017; Fitzhugh et al 2017; Hsieh et al 2014), outcomes reported by each of the three studies are shown in the evidence table.

1. Is HSCT clinically effective in the treatment of adults (aged 18 years and older) with SCD?

No studies compared HSCT with alternative treatment strategies.

Clinical outcomes reported in the five uncontrolled studies included overall survival, event-free survival, disease-free survival, non-relapse mortality, engraftment, chimerism, quality of life,

immunosuppression, hospitalisation, blood transfusion requirement, and narcotic need.

Overall survival
Overall survival was reported by four studies which included a total of 227[26] adults (range 20 to 154) (Ozdogu et al 2018; Gluckman et al 2017; Fitzhugh et al 2017; Hsieh et al 2014). 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)[27] in a study of HLA-identical donors (Hsieh et al 2014); neither or these studies reported 95% confidence intervals.

Event-free survival[28]
Event-free survival was reported by one study of HSCT using HLA-identical donors and which included 154 adults with SCD (Gluckman et al 2017). The five-year probability of event-free survival in the adult population was 81% (95%CI 74% to 87%) at a median follow-up of 48.0 months (range 2.18 to 305.9).

Disease-free survival
Disease-free survival was reported by three studies which included a total of 73 adults (range n=20 to n=30) (Ozdogu 2018; Fitzhugh 2017; Hsieh 2014). This ranged from between 35% to 50%[29] in one study of HSCT using haploidentical donors and median follow-up 3.17 years (range 0.67 to 6.16) (Fitzhugh et al 2017) to 100% at one year post-transplantation in a second study (Ozdogu et al 2018) using HLA-identical donors. The third study, of HSCT using HLA-identical donors, reported disease free survival of 87% after median follow-up of 3.4 years (range 1 to 8.6)[24] (Hsieh et al 2014).

Non-relapse mortality
Non-relapse mortality was reported by two studies, including a total of 50 adults, both involving HSCT using HLA-identical donors. One study (Ozdogu et al 2018) (n=20) reported that no patients had died after one year of follow-up; the other study (Hsieh et al 2014) (n=30) reported that no patients had died without relapse or recurrence by the study endpoint, after median follow-up of 3.4 years (range 1 to 8.6)[24].

Engraftment
Engraftment was reported by four studies which together reported data on 73[30] patients (range of individual studies n=20 to n=61) (Ozdogu et al 2018; Allen et al 2017; Fitzhugh et al 2017; Hsieh

[26] 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
[27] 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)
[28] Defined by Gluckman et al (2017) as the probability of being alive with sustained donor cell engraftment
[29] 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%
[30] 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 with β-thalssaemia) and Hsieh et al (2014) (n=29 adults with SCD, n=1 with β-thalssaemia) 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

et al 2014). Outcome measures varied between studies and included: proportion of patients with engraftment at specified time points; proportion with sustained/long-term engraftment at study endpoint, and mean time to engraftment.

The proportion of patients with sustained engraftment ranged from 77% (n=47/61) in adults with SCD who had HSCT from mixed-type donors[31] (median follow-up 4.3 years (IQR 1.8 to 5.8)) (Allen et al 2017) to 87% (n=26/30) in a study of HSCT using HLA-identical sibling donors (Hsieh et al 2014) which included one patient without SCD; median follow-up was 3.4 years (range 1 to 8.6). Fitzhugh et al (2017) reported that 70% (16/23) of patients achieved engraftment by 100 days post-transplantation using haploidentical donors. Mean neutrophil engraftment time[32] was reported as 18 days (range 13 to 22) in one study using HLA-identical donors, in which 100% of patients had neutrophil engraftment at 30 days (Ozdogu et al 2018). In a second study (Allen et al 2017), of HSCT using donors of mixed type, mean time to engraftment was 18.45 days (± SD 7.21) and median time to engraftment was 14 days (range 13 to 43).

Chimerism

Donor chimerism was reported (as total cell chimerism and/or by cell lineage) by three studies which included 73 adults (range n=20 to n=30) (Ozdogu et al 2018; Fitzhugh et al 2017; Hsieh et al 2014). Full donor chimerism at one year post-transplantation ranged from 83% (Hsieh et al 2014) to 100% (Ozdogu et al 2018), both studies of HSCT using HLA-identical donors; no patients achieved full donor chimerism in a third study using haploidentical donors (Fitzhugh et al 2017) at median follow-up 3.17 years (range 0.67 to 6.16). Mean donor myeloid-cell chimerism ranged from 84.8% (±SE 8.8) in a study of HSCT using haploidentical donors (Fitzhugh et al 2017) to 86% (95%CI 70% to 100%) in a study of HSCT using HLA-identical donors (Hsieh et al 2014). Mean T-cell chimerism, reported by one study, was 48% (95% CI 34% to 62%) at median follow-up of 3.4 years (range 1 to 8.6)[24] after HSCT using HLA-identical donors (Hsieh et al 2014).

Quality of life

One study, which included 20 adults with SCD, measured quality of life using the short form SF-36 before and one year after transplantation using HLA-identical donors(Ozdogu et al 2018). There was a statistically significant improvement in the post-transplantation scores at one year in two SF-36 domains: health general (before transplantation 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-transplantation scores but the difference between before and after transplantation scores was not statistically significant. No results were reported for the SF-36 physical functioning domain.

Immunosuppression

Two studies, which included a total of 50 adults (n=20 and n=30), reported immunosuppression in terms of either the proportion of patients who had stopped taking immunosuppressants by a specified time point (Ozdogu et al 2018) or the duration of immunosuppressant medication post-transplantation (Hsieh et al 2014); both studies involved HSCT using HLA-identical donors. At one year post-transplantation, 92% (12 of 13 patients who had completed one year follow-up, equivalent to 60% of the total study population), had stopped taking immunosuppressants (Ozdogu et al 2018). In the study by Hsieh et al (2014), median duration of immunosuppression

(n=19 vs n=21 in Fitzhugh et al). The level of overlap between the Hsieh et al study and Allen et al study is not clear from the two published studies.

[31] HLA-identical or HLA-haploidentical

[32] Defined as the first of three consecutive days on which the absolute neutrophil count exceeded 0.5×10^9 cells/L

post-transplantation was 2.1 years (range 1.0 to 8.4), and 50% of patients (n=15) continued without taking immunosuppression[33] (median follow-up 3.4 years (range 1 to 8.6)[24]).

Hospitalisation

Two studies, which included a total of 50 adults (n=20 and n=30), reported hospitalisation rates before and after transplantation using HLA-identical donors. In one study, of 20 adults with SCD (Ozdogu et al 2018), 90% of patients had at least one hospital admission per year before transplantation; after transplantation, the proportions of patients with at least one hospital admission 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. In the second study, of 30 adults (Hsieh et al 2014), the mean annual hospitalisation rate[34] (reported as number of hospitalisations per patient per year) for the year pre-transplant was 3.23[35] (95%CI 1.83 to 4.63). For the first, second and third years post-transplant, the mean annual hospitalisation rates were: 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.

Blood transfusion requirement

Two studies reported red blood cell transfusion requirement before and after transplantation including a total of 91 adults (n=30 and n=61) (Hsieh et al 2014; Allen et al 2017). In the study by Hsieh et al 2014, of HSCT using HLA-identical donors, 53% (n=16) patients had received previous simple/exchange red blood cell transfusions before transplantation (number/frequency not stated); after transplantation, 3% (one patient[36]) 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 of 3.4 years (range 1 to 8.6)[24]. The second study by Allen et al 2017, involving HSCT using either HLA-identical or haploidentical donors, did not report blood transfusion requirements in comparable units pre- and post-transplantation. Before transplantation, 46% of patients required more than 50 units of transfused red blood cells, 34% required 11 to 50 units, and 11% required one to 10 units[37]; after transplantation, amongst 47 patients with sustained engraftment (equivalent to 77% of total study population, n=61), median time to transfusion independence was 19 days (range 0 to 753).

Narcotic use

Narcotic use was reported by two studies including a total of 50 adults (n=20 and n=30) who received HSCT from HLA-identical donors. In one study (Ozdogu et al 2018), 85% of patients were using narcotics[38] before transplantation; at 100 days, 180 days, and one year after transplantation, the proportions of patients using narcotics were: 10% (n=2 of 20); 5% (n=1 of 16) and 0% (n=0 of 12) respectively. In the second study by Hsieh et al (2014), 37% (n=11 of 30) patients were on long-term narcotics[39] at baseline; mean narcotics use per week at time of transplantation was 639 mg (95%CI 220 to1058), and six months after transplantation was 140 mg (95%CI 56 to 225). Six patients (55% of those on long-term narcotics at baseline) were successfully weaned from long-term narcotics use after transplant; median follow up was 3.4

[33] 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%

[34] 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 so have been estimated for the purposes of this evidence table

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

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

[37] Transfusion requirement not known in a further 8% of patients

[38] Not defined

[39] Taking long-and short-acting narcotics for at least three months

years (range 1 to 8.6)[24]. Neither study reported any p values.

2. What is the safety profile for the use of HSCT in adults (aged 18 years and older) with SCD?

No studies compared HSCT with alternative treatment strategies.

Safety outcomes reported in the five included studies included graft failure and/or rejection, graft versus host disease, painful crisis, post-transplant infections, non-infectious transplant-related complications, large volume phlebotomy (for iron overload), and end-organ function (cardio-pulmonary, central nervous system, hepatic, and renal).

Graft failure and/or rejection[40]
Graft failure (engraftment/primary graft failure and/or secondary graft failure/rejection; median time to graft failure/rejection) was reported by the same four studies which reported engraftment (above).

In Allen et al (2017), graft failure occurred in 23% (n=14/61) of patients overall (after HSCT using HLA-identical or haploidentical donors); 7% (n=4/61) of patients had engraftment/primary graft failure, and 16% (n=10/61) had secondary graft rejection[41]. In Fitzhugh et al (2017), graft failure occurred in 65% (n=15/23) of the total study population (including two patients without SCD) after HSCT from haploidentical donors; primary graft failure occurred in 30% (n=7/23) of patients, and secondary graft failure occurred in 35% (n=8/23) patients. In Hsieh et al (2014), there were no patients with engraftment/primary graft failure after HSCT using HLA-identical donors. 13% (n=4/30) of study participants (including one without SCD) had temporary donor engraftment for one to three months after HSCT, then (secondary) graft failure and subsequent autologous recovery. In Ozdogu et al (2018), no patients (n=0/20) had (secondary) graft failure/rejection at one and two years post-transplantation from HLA-identical donors.

Median time to secondary graft failure/rejection (where reported) ranged from a median of 93.5 days (range 50 to 215) post-transplantation (Allen et al 2017) to 108.5 days (range 63 days to 2.35 years) (Fitzhugh et al 2017).

Graft versus host disease (GvHD)
GvHD (acute and/or chronic) was reported by four studies which included a total of 237 adults (Ozdogu et al 2018; Gluckman et al 2017; Fitzhugh et al 2017; Hsieh et al 2014). The cumulative incidence of acute GvHD ranged from 0% in a study with median follow-up 3.4 years (range 1 to 8.6) using HLA-identical donors (Hsieh et al 2014), to 9% in a second study with median follow-up 3.17 years (range 0.67 to 6.16) using haploidentical donors (Fitzhugh et al 2017). Gluckman et al (2018), did not publish acute GvHD results separately for adults but reported that the 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). This study population was heterogeneous in terms of stem cell origin, donor type and conditioning regimens used for HSCT.

[40] 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.
[41] Defined by Allen et al (2017) as the date on which chimerism studies showed no detectable donor CD3 or myeloid cells

The cumulative incidence of chronic GvHD ranged from 0% in two studies (Ozdogu et al 2018; Hsieh et al 2014), both involving HLA-identical donors, to 19.6% (95%CI 13.3% to 26.8%) in a study involving heterogeneity of HSCT approaches (Gluckman et al 2017). Five-year probability of GvHD-free survival[42] was 77% (95% CI not reported) (Gluckman et al 2017).

Painful crisis

Painful crisis was reported by one study of 20 adults with SCD (Ozdogu et al 2018). Before transplantation involving HLA-identical donors, 90% of patients suffered painful crises (number/frequency not reported); after transplantation (at 100 days, 180 days, and one year), no patients had a painful crisis. No p values were reported.

Transplant-related infections

Transplant-related infections were reported by three studies which included a total of 73 adults (range n=20 to 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[43] ranged from 27% (n=8/30) in a study using HLA-identical donors (Hsieh et al 2014)[44] 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 (other than infections)

Transplant-related complications (other than infections and changes in end-organ function) were reported by four studies which included a total of 134 patients (range 20 to 61) (Ozdogu et al 2018; Allen et al 2017; Fitzhugh et al 2017; Hsieh et al 2014).

The largest study (Allen et al 2017), of 61 adults with SCD with HLA-matched or haploidentical donors, reported immunohaematological complications only. These occurred in 15% (n=9/61) patients by the study endpoint (median follow-up 4.3 years (IQR 1.8 to 5.8)) and were associated with significant clinical events in five patients (8% of total study population): prolonged reticulocytopenia (n=3) and acute haemoloysis with severe anaemia (n=2). By the study endpoint, seven of the nine patients were still alive, two had died (one from lower gastrointestinal haemorrhage 4.5 years post-transplantation, the other from sepsis five years post-transplantation, after losing their graft during the first year post-transplant (day 214)).

Amongst the other three studies, one study (Ozdogu et al 2018) of HSCT using HLA-identical donors reported that all HbS trait patients (n=10, 50% of the study population) and all non-HbS trait donors (n=10) 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. In the second study, complications occurred in 61% (n=14 of 23 patients[45]), after HSCT using haploidentical donors (Fitzhugh et al 2017). In the third study, involving HLA-identical donors, all patients (n=30[46]) experienced at least one severe adverse event (SAE); a total of 38 SAEs were reported, of which six were for infections[47] (Hsieh et al 2014). The most common SAEs reported by Hsieh et al (2014) were classed as 'pain and related management' (for example, arthralgias, myalgias, and narcotics withdrawal).

[42] Defined as the probability of being alive without having experienced either grade III or grade IV aGVHD or extensive cGVHD
[43] As opposed to bacteraemia or febrile neutropenia with no diagnosed/suspected specific infection
[44] Six infections were recorded as serious adverse events (SAEs)
[45] Including two patients with β-thalassaemia and not SCD
[46] Including one patient with β-thalassaemia, not SCD
[47] Hsieh et al's (2014) reporting of SAEs included infections; the number/proportion of SAEs not involving infections were not separately reported

Changes in end-organ function (hepatic, renal, cardiopulmonary, central nervous system)
Two studies reported changes in end-organ function and included a total of 50 adults (n=20 and 30) (Ozdogu et al 2018; Hsieh et al 2014). Both studies involved HSCT from HLA-identical donors.

Ozdogu et al (2018) reported changes in **hepatic function**. These included, in 8/20 (40%) participants, temporary rises in levels of serum aminotransferase; these were up to three times higher than normal values at around one month and persisted for up to two months. Hepatic function was also reported by 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 patients had high ferritin levels greater than 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.

Hsieh at al (2014) reported that, before transplantation, 4/30 (13%) participants had sickle nephropathy (serum creatinine ≥ 1.3mg/dL). No worsening of a previously established decline in **renal function** was observed post-transplant.

Hsieh et al (2014) also reported changes in **cardiopulmonary function**. At baseline, 13/30 (43%) patients had a tricuspid regurgitant velocity (TRV) of more than 2.5 metres per second (m/s). The mean TRV pre-transplant was 2.84m/s (95% CI 2.71 to 2.99). This fell to 2.57m/s (95% 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 after transplant (n not stated) and to 2.33m/s (95% CI 2.14 to 2.51) at three years after transplant (n not stated, p values not reported clearly). Hseih et al (2014) also reported results of the mean six-minute walk test. Before transplant, mean distance walked was 455m (95% CI 244 to 665) in six minutes; one year post-transplant it was 504m (95% CI 206 to 801), and three years after transplant it was 507m (95% CI 332 to 681) (p=0.41).

Finally, Hseih et al (2014) reported **CNS function**. There were 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 two self-limited episodes at two and three months post-transplant.

Large volume phlebotomy
One study reported large volume phlebotomy (for the treatment of iron overload). In this study (Hsieh et al 2014), which included 30 adults (29 patients with SCD and one with β-thalassaemia) receiving HSCT from HLA-identical donors, 43% of patients required large volume phlebotomy 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 was 3.4 years (range 1 to 8.6)[24].

3. Is HSCT a cost-effective treatment option for use in adult patients with SCD?

No studies were identified reporting the cost-effectiveness of HSCT in adults with SCD.

4. From the evidence, are there any subgroups (e.g. those with a sibling donor) where HSCT is more clinically effective than in the wider SCD population?

There are some apparent differences in outcomes (eg survival and graft failure) reported for patients with different donor types (haploidentical vs HLA-identical). However, these findings are difficult to interpret because of significant confounding since they are reported by different uncontrolled studies using differing HSCT nMAC regimens in unmatched populations.

One study (Allen et al 2017) published data[48] on HSCT outcomes (engraftment/primary graft failure, secondary graft rejection, graft maintained long-term) in adults with SCD according to donor type (HLA-identical versus haploidentical).

Total graft failure (primary and secondary) rates in each group were: 12% (n=5/42) for patients with HLA-identical donors (similar to the 13% (n=4/30[49]) reported by Hsieh et al (2014) which investigated HSCT using HLA-identical donors), and 47% (n=9/19) for patients with haploidentical donors (compared with 65% (n=15/23[50]) reported by Fitzhugh et al (2017) which studied HSCT using haploidentical donors). Engraftment (primary graft) failure occurred in no patients (n=0/42) with HLA-identical donors (similarly, Hsieh et al (2014), reported no patients with primary graft failure), and in 21% (n=4/19) of those with haploidentical donors (compared with 30% (n=7/23) primary graft failure reported by Fitzhugh et al (2017)). Secondary graft rejection was reported in 12% (n=5/42) of patients with HLA-identical donors (compared with 13% (n=4/30[51]) reported by Hsieh et al (2014)) and 26% (n=5/19) of patients with haploidentical donors (compared with 35% (n=8/23) reported by Fitzhugh et al (2017). No p values were reported. Median follow-up was 1575 days (IQR 516 to 1831), equivalent to around 4.3 years (IQR 1.8 to 5.8).

Allen et al (2017) published baseline characteristics for the total study population and, separately, for patients receiving HSCT from haploidentical donors compared with those who had HLA-identical donors. Patients with haploidentical donors had a higher median age (36.3 years (IQR 27.1 to 39.8) vs 29.0 years (IQR 23.6 to 37.2)), a higher number/proportion who required more than 50 units of RBC transfusions pre-enrolment in the study (68% (n=13/42) vs 36% (n=15/19)), and a higher requirement for RBC transfusions post-enrolment[52] (median 20 units (IQR 16 to 29) vs 12 units (IQR 10 to 18)). These differences suggest that the patients receiving HSCT from haploidentical donors may have had higher morbidity associated with SCD at baseline compared with those who had HLA-identical donors. It is therefore difficult to interpret the differences in reported outcomes between the two groups. Median follow-up after HSCT was shorter for patients receiving HSCT from haploidentical donors than for those with HLA-identical donors (median follow-up 1021 days (IQR 499 to1341) vs 1764 days (IQR 565 to1991), equivalent to 2.79 vs 4.83 years, respectively).

The two studies by Fitzhugh et al (2017), using haploidentical donors, and Hsieh et al (2014), using HLA-identical donors, both published additional outcomes which were not covered by Allen et al (2017). These included: overall survival (87% vs 97% respectively), disease-free survival (35% to 50% vs 87%), engraftment (70% at 100 days vs 100% at 30 days), cumulative incidence of GvHD (9% vs 0%) and transplant-related diagnosed infections (57% vs 27%). However, these findings are difficult to interpret due to significant confounding associated with, for example, differences in HSCT approach and population characteristics between the two studies.

[48] In tabular form only (Table 1, page e555, Allen et al 2017)
[49] Study population included one patient without SCD
[50] Study population included two patients without SCD
[51] Study population included one patient without SCD
[52] Not further defined

One study (Gluckman et al 2017) included adults (aged at least 16 years) with SCD who had received HSCT using PB stem cells (n=43, 28%) or BM stem cells (n=111, 72%). The outcomes, event-free survival and overall survival, were compared between PB and BM groups for the total study population (including children) but the analysis was not conducted separately for the adult population. All other studies included in this review involved HSCT using PB stem cells only.

None of the other included studies investigated whether the clinical effectiveness of HSCT varied for different subgroups of adults with SCD.

5 Discussion

This review has included five uncontrolled studies of HSCT in adults with SCD with study populations ranging from 20 to 154.

Three of the included studies were retrospective. The largest study (Gluckman et al 2017) was a review of international registry data on 154 adults (aged ≥16 years) (and 846 children <16 years) with SCD who received HSCT using HLA-matched sibling donors; no details were provided on type/severity of SCD amongst participants and HSCT approaches varied (eg in stem cell source, conditioning type/regimens, GvHD prophylaxis). The second largest study (Allen et al 2017) reported data, predominantly on immunohaematological complications post-HSCT, in 61 participants drawn from three NIH trials conducted at one US centre; all three trials were described as single arm, phase 1 and 2 studies of HSCT using PB stem cells and non-myeloablative conditioning regimens in patients with haemoglobinopathies (89% HbSS; the rest HbSC or HbS-β thalassaemia). The smallest study (Ozdogu et al 2018) involved 20 adults with severe SCD (85% HbSS, 15% HbS β-thalassaemia), all of Eti-Turk origin, treated consecutively at one centre in Turkey; HSCT involved PB stem cells, a non-myeloablative conditioning regimen and HLA-matched related donors (50% non-HbS trait donors, 50% HbS trait donors).

Two of the included studies were prospective. One study (Fitzhugh et al 2017) was a small, prospective dose escalation trial of HSCT using PB stem cells, three different doses of post-transplant cyclophosphamide, a non-myeloablative conditioning regimen and haploidentical related donors in 23 adults, 21 of whom had SCD; most participants had severe disease-related complications and/or comorbidity at baseline. The second study (Hsieh et al 2014) was a small prospective trial of HSCT using PB stem cells, a non-myeloablative conditioning regimen and HLA-matched related donors in 30 adults, 29 of whom had SCD, all with severe disease. Both studies were amongst the three NIH trials for which results were also reported by Allen et al (2017), but with different study end dates. Allen et al (2017) also included patients from a third NIH study which has not yet been published in a peer-reviewed journal. The Allen et al (2017) study reported results separately for adults with SCD whereas the Fitzhugh et al (2017) and Hsieh et al (2014) studies reported results for all patients including a few (n=2 in the Fitzhugh study, n=1 in the Hsieh study) who had β-thalassaemia but not SCD

The results from the included studies in this review suggest that HSCT in adults with SCD, after median follow-up of three to four years, is associated with the following outcomes: overall survival of at least 81%; event-free survival of 81%; disease-free survival of between 35% and 87%, and non-relapse mortality of 0%. Other outcomes include: sustained engraftment in 77% to 87% of participants, statistically significant improvements in two of eight SF-36 quality of life domains at one year (although the clinical significance of these is unclear), and cessation of immunosuppressant medication. Studies also reported reductions in narcotic use, hospitalisation rates, painful crises and blood transfusion requirements, and (where reported by one study)

improvements in measures of cardiopulmonary function post-HSCT, although again the clinical significance of this was unclear. Adverse events following HSCT are common and included: graft failure in 23% to 65% of patients; acute GvHD in up to 9% and chronic GvHD in up to 20% of patients; between 27% and 57% of patients had infections post-HSCT. Other complications were also common with 50% to 100% of patients having other side effects, some of which were life-threatening. Two studies reported transient changes in liver enzymes post-HSCT.

A major limitation of the evidence in this review relates to the design of included studies, all of which were uncontrolled, with a significant risk of bias. The studies were heterogeneous in terms of study populations and HSCT approach. Most of the studies included patients with severe SCD (the majority with HbSS), with differing inclusion criteria; the two largest studies did not provide any information on type/severity of SCD of participants. The approach to HSCT varied between studies in terms of: type of conditioning (myeloablative vs reduced intensity); combinations of drugs used in conditioning; level of total-body irradiation; GvHD prophylaxis, and type of donor (HLA-identical vs halpoidentical; related vs unrelated). Another important limitation of the included studies is that the longest median follow-up was less than five years and long-term outcomes are not reported. None of the studies included any data on costs associated with HSCT or standard care for adults with SCD.

The three studies reporting findings from the NIH trials all reported total graft failure but there were notable differences between them. For patients receiving HSCT using haploidentical donors, Fitzhugh et al (2017) reported total graft failure as 65% (n=15/23) for a study population which included 21 SCD patients and two β-thalassaemia patients. In contrast, Allen et al (2017) reported total graft failure as 47% (n=9/19) for SCD patients who had HSCT using haploidentical donors who were drawn from the same NIH trial population as Fitzhugh et al (2017). The reasons for the lower graft failure rate reported by Allen et al are not clear but may be linked to the fact that this study reported a subset (n=19) of the Fitzhugh data (n=23) and excluded data relating to two patients with β-thalassaemia who may have had worse outcomes. For SCD patients who received HSCT using HLA-identical donors, Allen et al (2017) reported total graft failure as 12% (n=5/42). This was similar to the total graft failure rate of 13% (n=4/30) reported by Hsieh et al (2014) which included data relating to one patient with β-thalassaemia alongside 29 patients with SCD. While the Allen et al (2017) results suggest that SCD adults receiving HSCT using haploidentical donors may have higher rates of total graft failure than those using HLA-identical donors (47% vs 12%), the patients receiving HSCT from haploidentical donors appeared to have had higher morbidity associated with SCD at baseline compared with those who had HLA-identical donors. In addition, the Allen et al (2017) study included data from a third NIH trial, also of HLA-identical donor transplants in SCD; the results of this trial have not yet been published in a peer reviewed journal so the data reported by Allen et al (2017) for this patient group may be unreliable.

It is therefore difficult to interpret the significance of different study findings on total graft failure because of lack of clarity on the patient groups included, baseline differences between patients receiving HSCT from HLA-identical and haploidentical donors, and the inclusion of data from a study which has not been peer reviewed.

Generalisability of study results to the management of SCD patients in England is limited by factors such as the lack of information on type/severity of SCD in the larger two studies and possible differences in HSCT regimens and approach to management of SCD between those used for the included study populations and patients treated by the NHS in England. One study was conducted in Turkey in a population of Eti-Turk origin (Ozdogu et al 2018)

Overall, the results from the included studies suggest that HSCT in adults with SCD is associated with five-year overall survival and five-year event free survival of more than 80%. Improvements in some other outcome measures after HSCT compared with pre-transplant, such as quality of life and a reduction in requirements for treatment with immunosuppressants, blood transfusions and narcotics, were also reported in some of the studies. However, the intervention is also associated with a risk of adverse events, including GvHD and other complications (infections and other), many of which are serious and may be fatal. Follow-up in all the included studies was less than five years so no information was available on long-term outcomes for patients undergoing HSCT. Since the studies were uncontrolled, it is not possible to compare the outcomes following HSCT with alternative treatment approaches.

There is a need for randomised controlled studies which compare the outcomes, costs and patient experience of HSCT with those of standard care in adults with SCD and include the assessment of long-term as well as shorter-term outcomes.

6 Conclusion

There are apparently no controlled studies of the effectiveness of HSCT for SCD in adults. The best available evidence comes from uncontrolled studies. This review identified three retrospective and two prospective uncontrolled studies with 20 or more adult subjects published in the last 10 years, the largest of which included 154 adults with SCD.

The largest study, which involved heterogeneity of approaches (in terms of stem cell origin, donor type and conditioning regimen), suggests that HSCT in adults with SCD may be associated with more than 80% overall survival at five years and more than 80% event-free survival at five years (although the number of patients alive at different time points was not reported for this study). However, the intervention is also associated with severe complications, some of which are associated with increased mortality.

There are some apparent differences in outcomes reported for patients with different donor types but the findings are difficult to interpret because of significant confounding. For example, overall survival was 87% in a study of HSCT using only haploidentical donors (Fitzhugh et al 2017) and 97% in a second study using HLA-identical donors (Hsieh et al 2014), and rates of total graft failure were higher in patients with haploidentical donors than those with HLA-identical donors (47% vs 12%, as reported by Allen et al 2017). However, published data on baseline characteristics (Allen et al 2017) suggests that patients with haploidentical donors in these studies may have had higher morbidity associated with their SCD at baseline than those with HLA-identical donors. Furthermore, the studies by Fitzhugh et al (2017) and Hsieh et al (2014) did not report results separately for patients with SCD but also included data for patients with β-thalassaemia which limits the conclusions that can be drawn from these two studies.

Patients with SCD have reduced life expectancy and are at risk of severe complications and morbidity as a result of their condition. Patients, their families/carers, and their clinicians need reliable information about the benefits and costs of different treatment approaches on which to base decisions about management of the condition. The studies included in this review indicate that HSCT is a feasible treatment for SCD in adults, and indicate the range of outcomes that may follow its use. However, they provide no information on the effectiveness of HSCT compared to alternative treatment strategies.

7 Evidence Summary Table

For abbreviations see list after each table

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Ozdogu et al 2018	S2 Retrospective case series of consecutive patients treated at 1 centre in Turkey between 2013 and 2017	n=20 All patients of Eti-Turk origin with homozygous HbS (n=17) or heterozygous combinations of HbS and thalassemia (HbS -ß thalassemia, HbS -a thalassemia) (n=3) Mean age 33.4 (range 20-45) years Male n=13	HSCT using PB stem cells (referred to as allo-PSCT) HLA-matched related donors: HLA10/10-matched HbS trait (n=10); HLA 10/10 matched non-HbS trait (n=10) Non-myeloablative conditioning regimen: Flu 150/Bu 3.2/Cy 29/ATG 30(Fresenius)/ TBI 200 followed by post-transplant	Primary Clinical effectiveness	Overall survival	At 1 year, n=20 (100%)	5/10	Direct	This small, uncontrolled retrospective study included patients treated at 1 centre in Turkey over a 4 year period Consecutive patients were enrolled in the study so reducing the possibility of selection bias associated with the retrospective design. The study population included 17 patients with homozygous HbS and 3 with heterozygous HbS and thalassaemia; results were reported for all patients together. Data were obtained from data collection forms designed for use with transplant patients. All data were verified by an independent data audit group Mean follow-up was 13.8 months (range 0.3 - 50), with more than one year follow-up in n=13[54] (65%) patients. Median follow-up not reported. Most outcomes were only reported at 1 year follow-up (or shorter). Cumulative incidence of graft rejection was reported at both1 and 2 years. 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
				Primary Clinical effectiveness	Disease free survival[55]	At 1 year, n=20 (100%)			
				Primary Clinical effectiveness	Non-relapse mortality[56]	At 1 year, n=0 (0%)			
				Primary Clinical effectiveness	Engraftment[57]	Neutrophil engraftment[58] at 30 days: n=20/20 (100%) Mean neutrophil engraftment time[59]: 18 (range 13-22) days			
				Primary Clinical effectiveness	Graft rejection	At 1 and 2 years, n=0 (0%)			
				Primary	Donor chimerism	Full donor chimerism (total cell) within 180			

[54] Inconsistency in reporting of the number of patients who completed 12 months' follow-up: reported as 13 in text of full paper (page 884), as 12 in abstract

[55] Not further defined

[56] Not further defined

Use of HSCT for adults with SCD (no comparator)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		(65%); female n=7 (35%)	Cy/sirolimus[53] as GvHD prophylaxis	Clinical effectiveness		days, n=20 (100%); sustained at 1 year, n=20 (100%)			
				Primary Clinical effectiveness	Graft versus Host disease	Cumulative incidence of acute GvHD[60] at 100 and 180 days: Grade II-IV: n=1 (5%) Grade III-IV: n=0 (0%) Cumulative incidence of chronic GvHD[61] at 1 year: n=0 (0%)			
				Primary Clinical effectiveness	Immunosuppression	At 1 year, n=12 patients had stopped taking immunosuppressants (of 13 patients (92%) who completed 1 year follow-up, equivalent to 60% of total study population (n=20))			
				Primary Clinical	Hospitalisation	Proportion of patients with hospitalisation rate ≥1 per year:			

[57] Study authors defined successful engraftment as normalization of cell counts in the peripheral blood, absence of HbS in patients who received stem cells from a non-HbS trait relative donor, <40% Hgb S (relative to total Hgb) in patients who received product from an HbS trait donor, and full total peripheral blood cell chimerism within days

[58] Study authors intended to report both neutrophil and platelet engraftment time; however, platelet engraftment time could not be evaluated as platelet count did not decrease <30,000/µL during transplant procedure

[59] Defined as the first of 3 consecutive days on which the absolute neutrophil count exceeded 0.5×10^9 cells/L

[53] For immunosuppression

[60] Acute GvHD (aGvHD) was evaluated according to standard criteria (referenced but not further described)

[61] Diagnosis of chronic GvHD (cGvHD) made on the basis of both clinical and histology criteria of the skin and other affected sites; cGvHD was defined as any GvHD present after day 100

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				effectiveness		Pre-transplant:[62] n= 18/20 (90%) Post-transplant (at 100 days, 180 days, 1 year): n=6/20 (30%); n=4/16 (20%); n=1/12 (5%) respectively p values not reported			
				Primary Clinical effectiveness	Painful crisis (≥2 per year)	Pre-transplant: n=18/20 (90%) Post-transplant (at 100 days, 180 days, 1 year): n=0/20 (0%); n=0/16 (0%); n=0/12 (0%) respectively p values not reported			
				Primary Clinical effectiveness	Narcotic use[63]	Pre-transplant: n=17/20 (85%) Post-transplant (at 100 days, 180 days, 1 year): n=2/20 (10%); n=1/16 (5%); n= 0/12 (0%) respectively p values not reported			
				Primary	Quality of life (self-reported	Domain scores pre-transplant and 1 year			

[62] Pre-transplant denotes approximately one month before HSCT
[63] Described by study authors as 'narcotic need', not further defined

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Clinical effectiveness	short form SF-36[64])	post-transplant (mean ± SD, p value for difference): Role physical 59.9 ± 14.2; 80.2 ± 23.7, p=0.059 Health general 21.0 ± 22.3; 71.9 ± 21.7, p=0.005 Bodily pain 30.6 ± 27.2; 93.9 ± 14.5, p=0.004 Energy/vitality 51.2 ± 27.2; 67.7 ± 21.3, p=0.061 Social functioning 38.9 ± 18.1; 55.9 ± 27.1, p=0.062 Role emotional 42.4 ± 39.7; 69.8 ± 23.1, p=0.095 Mental health 62.2 ± 20.2; 74.2 ± 17.4, p=0.072			

[64] Version 1.0 of the SF-36 (normalised to the values of the Turkish population at two time points: before HSCT and one year after HSCT). 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 (this domain was not reported by Ozdogu et al (2018); reasons for this were not stated); 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

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Primary Safety	Transplant-related side effects (non-infectious)	Side effects related to G-CSF and plasma apheresis (which included minor pain, headache, paraesthesia, fatigue) occurred in n=10 (100%) HbS trait patients, n=10 (100%); non-HbS trait donors Temporary serum aminotransferase level elevation up to 3 × higher than normal values at around 1 month, persisting for ≤ 2 months: n=8 (40%) Liver biopsy showing pathological evidence of drug effect: n=1 Hyperlipidaemia: n=3 (15%)			
				Primary Safety	Transplant-related infections	Febrile neutropenia: n=8 (40%) (in whom enterobacter faecium and klebsiella spp. were detected in n=2) CMV antigenaemia: n=5 (25%) BK virus (BKV)-related haemorrhagic cystitis: n=3 (15%) Herpes zoster: n=1 (detected 6 months post-transplant)			

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Pneumonitis: n=3 (15%) (associated with sirolimus use)			
Gluckman et al, 2017	S2 Retrospective study of international registry data[65] on recipients of HSCT (at first transplant) before 31 Dec 2013 (median year of HSCT in adults	n=154 adults (≥16 years) with SCD Median age 19.3 (range 16-54.4) years Male n=82 (53.2%); female n=72 (46.8%)	HSCT Source of stem cells: BM, n=111 (72%); PB, n=43 (28%) HLA-identical sibling donors Myeloablative conditioning[66] (n=113, 73%), most commonly Bu + Cy or Flu (n=83, 74%); stem cell source: BM	Primary Clinical effectiveness	Overall survival	5-year probability of OS: 81% (95%CI 74%-88%)	7/10	Direct	This was an uncontrolled retrospective review of registry data. The study population included children (n=846) as well as adults (n=154). Only results for outcomes that were reported separately for adults (defined by study authors as ≥16 years of age) are extracted here Median follow-up for adult (≥16 years) study population was 48.0 (2.18-305.9) months. Numbers of patients alive at different time points (at 1 year intervals from 0 to 10 years post-HSCT) were reported for total study population but not separately for adult (≥16 years) population The study authors report that the most frequent indications for HSCT in the study population (adults and children) were stroke, acute chest syndrome, and recurrent vaso-occlusive disease. Before transplant, most patients had been transfused and treated with hydroxyurea
				Primary Clinical effectiveness	Event free survival[67]	5-year probability of EFS: 81% (95%CI 74%-87%)			
				Primary Safety	Graft versus Host disease [68]	Risk for aGvHD[69]: higher with increasing age, HR 1.04; 95%CI 1.01-1.07, p=0.008 For every 1 year increment in age at HSCT, there was a 4% increase in HR for aGvHD Cumulative incidence of cGvHD: 19.6% (95%CI 13.3%			

[65] From Center for International Blood and Marrow Transplant Research (CIBMTR), European Society for Blood and Marrow Transplantation (EBMT), and Eurocord databases using data from 106 centres in 23 countries worldwide

[66] Conditioning regimen defined according to published criteria as myeloablative conditioning (MAC) if total-body irradiation (TBI) was higher than 6Gy and busulfan was higher than 8mg/kg with or without other drugs being used; conditioning was defined as reduced intensity conditioning if fludarabine (Flu) was associated with less than 6Gy TBI or busulfan 8mg/kg or less, melphalan 140mg/m^2 or less, or other non-myeloablative drugs. Data on conditioning regimen not reported for one adult patient

[67] Defined as the probability of being alive with sustained donor cell engraftment

[68] Defined according to standard criteria

[69] 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

Use of HSCT for adults with SCD (no comparator)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	2008, range 1989-2013)		n=89/113 (79%), PB in n=24/113 (21%) Reduced intensity conditioning (n=40, 26%), most commonly Flu ± other drug; stem cell source: BM in n=21/40 (52.5%), PB in n=19/40 (47.5%)			to 26.8%) 5-year probability of GvHD-free survival[70] for adult patients aged ≥16 years: 77%			Conditioning regimens varied and involved different combinations of drugs (including busulfan, cyclophosphamide, fludarabine); 21% (n=32) patients had regimens involving total-body irradiation; GVHD prophylaxis regimens also varied The retrospective design of the study introduces the possibility of selection bias in the study population associated with, for example, the completeness or classification of information from patient records Information on the study population characteristics was limited to demographic information (age, gender) only; no details were provided on type/severity of SCD which limits generalisability. The reported results include an unknown number of patients who were aged 16-17 years; median age of adult/adolescent population (aged ≥16 years) was 19.3 years. Heterogeneity in terms of stem cell source (BM in 72%, PB in 28%), conditioning type (MAC 73%, RIC 26%, other/missing data 1%) conditioning regimen (most commonly involving busulfan, fludarabine and/or cyclophosphamide) and GvHD prophylaxis (most commonly cyclosporin plus methotrexate) also limits generalisability Outcomes were not reported separately for any subgroups of the adult (aged ≥16 years) population. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments

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

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Allen et al, 2017	S2 Retrospective review of patients enrolled before 31 Mar 2015 (using data collected up to 31 March 2016) in 3 NIH clinical trials of non-myeloablative HSCT Single centre, US	n=61 adults (of 65[71] enrolled in three NIH trials) with haemoglobinopathy: HbSS n=54 (89%); HbSC n=3 (5%); HbS-βthalassaemia n=4 (7%) Mean age 32.5 years (SD 10.1); median age 31.2 years (IQR 24.4-37.8) Male n=34 (56%); female n=27 (44%)	HSCT[72] using PB stem cells HLA-identical donors, n=42 (69%); haploidentical donors, n=19 (31%) Non-myeloablative conditioning regimen: alemtuzumab with TBI (300 cGy or 400 cGy) followed by post-transplant Cy/sirolimus as GvHD prophylaxis	Primary Clinical effectiveness	Engraftment[73]	By study endpoint (median follow-up 1575 days (IQR 516 -1831)): Sustained engraftment Total n=47[74]/61 (77%); HLA-identical donor n=37/42 (88%); Haploidentical donor n=10/19 (53%) Time to engraftment : mean 18.45 days ± SD 7.21; median 14 days (range 13 - 43)	5/10	Direct	This was an uncontrolled retrospective review of data (collected up to 31 March 2016) from three clinical trials of HSCT for SCD using a non-myeloablative conditioning regimen and involving HLA-identical or haploidentical donors. The review focused primarily on immunohaematological complications after HSCT Mean follow-up was 1643 days (SD 907), equivalent to 4.5 years; median follow-up was 1575 days (IQR 516 -1831), equivalent to 4.3 years (IQR 1.8-5.8). Follow-up was shorter for patients with haploidentical donors than those with HLA-identical donors (median 1021 days (IQR 499 -1341) vs 1764 days (IQR 565-1991), equivalent to median follow-up 2.79 vs 4.83 years respectively) The retrospective design introduces the possibility of selection bias in the study population associated with, for example, the completeness or classification of information from patient records Two of the three NIH clinical trials on which this study is based have data published in peer reviewed journals and are included in this review (Fitzhugh et al 2017; Hsieh et al 2014);data from the third NIH trial are not yet published in a peer reviewed journal so may be unreliable . Allen et al included 19 adults with SCD who received HSCT using haploidentical donors and were in the same NIH trial as that
				Primary Clinical effectiveness	Graft failure or rejection	By study endpoint (median follow-up 1575 days (IQR 516 -1831)): Engraftment failure[75]: Total n=4/61 (7%); HLA-identical donor n=0/42 (0%); Haploidentical donor n=4/19 (21%) Secondary graft rejection[76]: Total n=10/61 (16%); HLA-identical donor			

[71] Amongst the other four of 65 patients enrolled in the three trials, n=1 died pre-transplant, n=3 had β-thalassaemia with no HbS genes
[72] Described by study authors as human progenitor cell (HPC) transplantation
[73] Not defined by study authors
[74] Includes three patients who showed signs of graft rejection and received repeat HPC transplantation boosts from their original donors
[75] Engraftment failure not defined
[76] Defined as the date on which chimerism studies showed no detectable donor CD3 or myeloid cells

Use of HSCT for adults with SCD (no comparator)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						n=5/42 (12%); Haploidentical donor n=5/19 (26%) Time to secondary graft rejection: mean 109.7 days; median 93.5 days (range 50 - 215)[77]			reported by Fitzhugh et al (n=21 adults with SCD, n=2 adults without SCD) but had an earlier study endpoint (31 March 2015 vs 13 May 2016). Allen et al also included 42 adults with SCD who received HSCT using HLA-identical donors, including patients who were in the same NIH trial as that reported by Hsieh et al (n=29 adults with SCD, n=1 without SCD) but with a later study endpoint (31 March 2015 in Allen et al vs 25 Oct 2013 in Hsieh et al). The extent of the overlap in reporting between the Allen et al study and the studies by Fitzhugh et al and Hsieh et al is not clear. Unlike Fitzhugh et al (2017) and Hsieh et al (2014) (see separate rows in this table), Allen et al (2017) report data relating only to adults with SCD from these two trials (and exclude data relating to patients who did not have SCD). They included 54 patients with HbSS, 3 with HbSC and 4 with HbS-βthalassaemia. All patients received a similar non-myeloablative conditioning regimen. Clinical effectiveness outcomes were generally better among patients receiving HSCT from HLA-identical donors vs those with haploidentical donors. However reported differences between patients receiving HSCT from haploidentical donors vs those with HLA-identical donors included: higher median age (36.3 years (IQR 27.1-39.8) vs 29.0 years (IQR 23.6 -37.2)); higher number/% requiring >50 units of RBC transfusions pre-enrolment (n=13/42 (68%) vs n=15/19 (36%)); higher requirement for RBC transfusions post-enrolment (median 20 units (IQR 16-29) vs 12 units (IQR10-18). These differences suggest that patients with HSCT from haploidentical donors had worse SCD than those with HLA-identical donors. It is therefore difficult to interpret
				Primary Clinical effectiveness	RBC transfusion	RBCs transfused: In total study population (n=61): RBCs transfused before enrolment: Unknown, n=5/61 (8%) 1-10 units, n=7/61 (11%) 11-50 units, n=21/61 (34%) >50 units 28/61 (46%) RBCs transfused after enrolment (n=61/61): Mean 20.0 units (SD 16.7) of which a mean of 12.3 units (SD 15.3) were transfused after transplant; Median 15 units (IQR 10-22) (post-transplant data not reported separately) In 47/61 patients with sustained engraftment:			

[77] All secondary graft rejections occurred between days 50 and 187, except for one on day 215

Use of HSCT for adults with SCD (no comparator)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						RBCs transfused after enrolment, mean 17.70 units, SD 16.64; median 12 units (range 7 - 99); Time to transfusion independence, mean 63.70 days, SD129.04; median 19 days (range 0 -753)			the differences in outcomes between the two groups reported in this paper. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments
				Primary Safety	Transplant-related complications (immunohaematological[78])	By study endpoint (median follow-up 1575 days (IQR 516 -1831)), complications reported in n=9 (15%) patients, in whom significant clinical events occurred in n=5 (8%): • prolonged reticulocytopenia, n=3 • acute haemoloysis with severe anaemia, n=2 By the study endpoint (median follow-up 1575 days (IQR 516 -1831)), 7 of the 9 patients were still alive, 2 had died from: • lower gastrointestinal			

[78] Defined as the formation of new red cell antibodies after haemopoietic progenitor cell (HPC) transplantation, the presence of red cell antibody and its cognate antigen in a donor-recipient pair, or both

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• haemorrhage (4.5 years post-transplant), n=1[79] • sepsis (5 years post-transplant, after losing graft on day 214), n=1			
Fitzhugh et al, 2017	P1 Prospective phase 1 and 2 dose escalation trial evaluating ability of PT-Cy to improve engraftment after haplo-identical HSCT Single centre, US	n=21 adults with SCD (of 23 enrolled[80]) (n=19 homozygous SCD, n=1 HbSC disease, n=1 HbS β^0-thalassaemia) Median age (full study population) 36 years (range 20-56) Male 12 (57%); female 9 (43%)	HSCT using PB stem cells Haploidentical donors (for n=21 SCD patients): 5/10 HLA-matched, n=5 (24%); 6/10 HLA-matched, n=4 (19%); 7/10 HLA-matched, n=7 (33%); 8/10 HLA-matched, n=5 (24%) Non-myeloablative regimen: alemtuzumab, 400 cGy total body	Primary Clinical effectiveness	Engraftment[83]	By 100 days post-transplant, total n=16/23[84] (70%) Cohort 1: n=1[85]/3 (33%) Cohort 2: n=5/8[86] (63%) Cohort 3: n=10/12 (83%)	6/10	Direct	This was an uncontrolled prospective trial in patients undergoing HSCT using PB stem cells from haploidentical donors, investigating the rate of engraftment associated with increasing doses of post-transplant cyclophosphamide in a non-myeloablative conditioning regimen. Results are presented for the total study population and for individual PT-Cy cohorts. Median follow up for total study population (n=23) was 3.17 years (range 0.67 - 6.16) 2 of 23 patients had β-thalassaemia, not SCD, but results were not reported separately by diagnosis. People without SCD may have a different risk profile and outcomes following HSCT compared to those with SCD Unclear reporting in terms of total number of patients with complications, the total numbers of patients and the number in each cohort at different time points.. It was not clear whether there were differences in characteristics between patients recruited to the 3 PT-Cy dosing cohorts.
				Primary Clinical effectiveness	Disease-free survival	By study endpoint (median follow-up 3.17 years (range 0.67 - 6.16), total n= 8/23 (35%) Cohort 1: n=0/3 (0%) Cohort 2: n=2/8 (25%) Cohort 3: n=6/12 (50%)			
				Primary Clinical effectiveness	Overall survival	By study endpoint (median follow-up 3.17 years (range 0.67 - 6.16), total n=20/23 (87%)			

[79] This patient was one of the three who had prolonged reticulocytopenia
[80] The other two of 23 patients enrolled in the study had β-thalassaemia

Use of HSCT for adults with SCD (no comparator)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	Results published for period up to 13 May, 2016	Most patients had severe disease-related complications and/or comorbidity at baseline: n=20 (87%) hepatic complication (including n=2 with cirrohosis); n=5 (22%) systolic dysfunction with LVEF ranging from 36-52%; n=3 (13%) diastolic dysfunction; n=6 (26%) severe renal	irradiation, escalating doses[82] of post-transplant cyclophosphamide (PT-Cy): 0mg/kg (cohort 1), 50mg/kg (cohort 2) and 100mg/kg (cohort 3)	Primary Clinical effectiveness	Donor chimerism (myeloid and CD3 cells)	By study endpoint (median follow-up 3.17 years (range 0.67 - 6.16), n=0/23 (0%) of all patients achieved complete (100%) donor chimerism[87] Mean % (± SE)donor myeloid chimerism and mean % (± SE) donor CD3 chimerism amongst patients who initially engrafted in each PT-Cy cohort: Cohort 1 (n=1): mean donor myeloid chimerism and mean CD3 chimersim at 12 months post-transplant were both 0% Cohort 2 (n=5): mean donor myeloid chimerism at 3 months,			Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments

[83] Not defined
[84] Results not reported separately by diagnosis so are shown here for the total study population (n=23)
[85] Patient rejected graft seven months post-transplant so stopping rules were reached and study was advanced to cohort 2
[86] Cohort 2 included two patients who had β-thalassaemia without HbS; no information was provided regarding diagnoses of the five patients in whom engraftment was observed; the three remaining patients in the cohort were determined to have insufficient donor chimerism at a median of 1.30 years (range 127 days to 2.35 years) post-transplant
[82] If the regimen failure rate exceeded predefined stopping boundaries in a cohort, accrual to that cohort was stopped and the study was advanced to the next dosing cohort
[87] Not defined

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		disease; n=5 (22%) pulmonary hypertension n=14 (61%) had ≥3 severe SCD-related complications or comorbidities at baseline Mean HCT-CI[81] score 6 ± 2.3 (n=17 had score ≥5, n=0 had score <2)				2 years, 3 years: 76% (±14.2), 33% (±17.0), 33.5% (±19.8); mean CD3 at same timepoints: 6.8% (±4.6), 16.2% (±5.8), 16.5% (±7.4) Cohort 3 (n=10): mean donor myeloid chimerism at 3 months, 6 months, 1 year, 2 years, 3 years (n=1): 52.1% (±14.4), 84.8% (± 8.8), 81.8% (± 9.5), 79.3% (±13.3), 52% (SE not reported); mean CD3 at 3 months, 2 years: 2.2% (±1.3), 57.7% (±14.2)			
				Primary Clinical effectiveness	Immunosuppression	By study endpoint (median follow-up 3.17 years (range 0.67 - 6.16), all engrafted patients were still receiving immunosuppression			
				Primary Clinical effectiveness	Graft failure[88] or graft rejection[89]	Graft failure: By study endpoint (median follow-up 3.17 years (range 0.67 - 6.16), n=7/23 (33%)			

[81] HCT-CI is the haematopoietic cell transplantation-specific comorbidity index and consists of 16 different comorbidities, including cardiopulmonary, renal, gastro-intestinal, and neurological comorbidities. The HCT-CI score was calculated by using an online web-based calculator (www.hctci.org)
[88] Graft failure (and terms primary and secondary graft failure) not defined by study authors
[89] Graft rejection is a major cause of graft failure and is due to recipient immune response against donor immunohaematopoietic cells; the term was not defined by the study authors

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						had primary graft failure; n=8/23 (38%) had secondary graft failure at median of 108.5 days (range 63 days to 2.35 years) Graft rejection: Total n=6[90]/23 (26%) Cohort 1: n=1/3 rejected graft at 7 months post-transplant Cohort 2: n=1/8 acutely rejected graft Cohort 3: 4/12 (33%) rejected graft at median of 73.5 days (range 63-90)			
				Primary Clinical effectiveness	GvHD[91]	In total n=3/23 (13%) developed GvHD Cohort 1: n=0/3 (0%) GvHD Cohort 2: n=1/8 (13%) questionable grade 1 aGvHD at 4 months post-transplant Cohort 3: n=1/12 (8%) grade 1 aGvHD which cleared with topical corticosteroids 3 weeks			

[90] Not specified whether this group was additional to, or a subset of, those patients who experienced graft failure
[91] GvHD, acute GvHD and chronic GvHD not defined by study authors

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						post-transplant, n=1/12 (8%) limited ocular cGvHD at 2 years post-transplant			
				Primary Safety	Transplant-related complications (other than infections)	Severe adverse events[92] possibly or definitely associated with sirolimus occurred in n=7/23 (30%) patients: bone or joint pain and/or swelling n=3; nausea and/or abdominal pain n=2; rhabdomyolysis n=1; recurrent gastric ulcer-associated bleeding n=1 (this patient, who also had end-stage renal disease , was transitioned to tacrolimus and then developed posterior reversible encephalopathy syndrome) A further n=4 (17%) patients had other possible sirolimus-associated complications not classed as severe			

[92] Severe adverse events were described by study authors as possibly or definitely as a result of sirolimus

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						adverse events: n=1 nephrotic syndrome peri-transplant; n=2 pneumonitis; n=1 diffuse alveolar haemorrhage). Other reported transplant-related complications, n=4 (17%): n=2 cardiac arrhythmias which did not required chronic therapy; n=2 high grade myelodysplastic syndrome with fibrosis (both died as a result of associated complications)			
				Primary Safety	Transplant-related complications (infections)	Numbers (%) of patients with infections: Bacteraemia which responded to antibiotics, n=15/23 (65%) Other infections reported, n=13/23 (57%): Adenovirus upper respiratory tract infection with transaminitis and viraemia, n=1 (4%) EBV-associated			

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						lympho-proliferative disorder, n=1 (4%) CMV reactivation, n=4 (17%) CMV colitis, n=1 (4%) Chronic EBV viraemia, n=3 (13%) Treatment for presumed fungal pulmonary nodules, n=3 (13%)			
Hsieh et al, 2014	P1 Prospective phase 1 and 2 study, enrolling patients from 16 July 2004 to 25 Oct 2013 (study endpoint for data collectio	n=30[93] (n=29 severe sickle cell phenotype, n=1 transfusion-dependent β-thalassaemia intermedia (Pesaro class 2)) Median age at transplant 28.5 (range 17-65) years	HSCT using PB stem cells HLA-matched sibling donors Non-myeloablative regimen: alemtuzumab (1mg/kg in divided doses), total-body irradiation (300 cGy), sirolimus, and infusion of	Primary Clinical effectiveness	Overall survival	By study endpoint (median follow-up 3.4 years (range 1 to 8.6), n=29 (97%) patients were still alive (n=1 patient died after relapse)	6/10	Direct	This was an uncontrolled prospective trial investigating treatment success at 1 year post-transplant in adult patients (aged 17-65 years) with SCD or thalassaemia using a non-myeloablative regimen and HLA-matched sibling donors Median follow-up reported inconsistently as 3.4 years (range 1[94] to 8.6) and as 3.6 years (range 1.0 to 8.4) 1 of 30 patients 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 Hospitalisation data may be unreliable; data for mean hospitalisation rates published in abstract only
				Primary Clinical effectiveness	Disease free survival	By study endpoint (median follow-up 3.4 years (range 1 to 8.6), n=26/30 (87%)			
				Primary Clinical effectiveness	Non-relapse mortality	By study endpoint (median follow-up 3.4 years (range 1 to 8.6), n=0 (0%)			
				Primary	Engraftment	By study endpoint (median follow-up 3.4			

[93] HLA typing was performed in n=287 patients and approximately 2 donors per patient, and HLA 6/6 match was found in n=102 patients; of these n=50 met eligibility criteria for HSCT. Of the 50 eligible patients, n=19 were still receiving optimising medical therapy prior to HSCT, n=30 received HSCT as assigned and n=1 died prior to HSCT.

[94] As reported

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	n) Single transplant centre, US	Male n=16 (53%); female n=14 (47%) Indications for transplant included end-organ complication or reversible complication not ameliorated by hydroxyurea n=22 (73%) had ≥2 indications or ≥1 comorbid condition n=28 (93%) had prior treatment with hydroxyurea	unmanipulated fligrastim mobilised PB stem cells (5.5 -31.7 ×10 ^{6} cells/kg)	Clinical effectiveness		years (range 1 to 8.6): Sustained donor leukocyte engraftment[95] n=26/30 (87%) Temporary donor engraftment for 1-3 months post-transplant, with subsequent graft rejection and autologous recovery with SCD[96] n=4/30 (13%)			and not in full paper; median hospitalisation rates published in chart only with data not separately reported. Since the study does not include a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments
				Primary Clinical effectiveness	Donor chimerism	At 1 year, n=25 (83%) full donor-type Hb At median follow-up 3.6 years: mean donor myeloid-cell (CD14 or CD15) chimerism: 86% (95%CI 70%-100%) mean T cell chimerism: 48% (95% CI 34%-62%) n=0 patients achieved 100% donor chimerism in both myeloid and T cell compartments; for both compartments,			

[95] Defined as full donor-type Hb on Hb electrophoresis
[96] One of these patients died from intracranial bleeding associated with previous moyamoya disease after relapse of SCD

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						plateau (for chimerism levels) was reached at 12 to 18 months post-transplant			
				Primary Clinical effectiveness	Immunosuppression	Median duration of immunosuppression post-transplant 2.1 years (range 1.0-8.4); n=15 (50%) continued without taking immunosuppression medication[97]			
				Primary Clinical effectiveness	Hospitalisation	Mean annual hospitalisation rate[98] (number per patient per year): For pre-transplant year: 3.23[99] (95%CI 1.83-4.63) Post-transplant (1st year, 2nd year, 3rd year): 0.63 (95%CI 0.26-1.01), 0.19 (95%CI 0-0.45), 0.11 (95%CI 0.04-0.19) respectively			

[97] 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%

[98] 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 so have been estimated for the purposes of this evidence table

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

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Primary Clinical effectiveness	Transfusion requirement	Pre-transplant, n=16 (53%) had simple/exchange red blood cell transfusions; post-transplant, n=1[100] (3%) needed transfusions for up to 1.5 years, achieving full donor red cell engraftment and transfusion free status at 2 years; no other patients were reported to have post-transplant transfusions			
				Primary Clinical effectiveness	Narcotic use	At baseline, n=11/30 (37%) on long-term narcotics[101] Mean narcotics use per week (mg intravenous morphine-equivalent dose (95%CI)): At time of transplant, 639 (220-1058); Post-transplant, at 6 months, 140 (56-225) p value not reported n=6 (55% of those on long-term narcotics) were successfully weaned from long-term narcotics use			

[100] Patient had detectable anti-Jka antibody to donor red blood cells pre-transplant
[101] Taking long-and short-acting narcotics for at least three months

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Primary Safety	Graft versus Host disease	n=0 developed acute or chronic GvHD (even after cessation of immunosuppressants in n=15); follow-up <2 years in n=3			
				Primary Safety	Transplant-related complications (infections and non-infectious)	n=0 (0%) acute SC-related complications Most patients (number not specified) reported to have sirolimus-related adverse events (eg arthralgia, hypertriglyceridaemia) during first 100 days post-transplant Infections (not reported as severe): n=24/30 (80%) febrile neutropenia treated with antibiotics; n=8/30 (27%) patients with diagnosed infections: • n=4 cases treated pre-emptively for CMV; • n=2 dermatomal zoster, • n=1 suspected herpes virus reactivation in GI tract,			

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• n=1 treated for presumed pulmonary antifungal infection (above 4 cases all occurred ≥1 year post-transplant) 38 SAEs[102] reported in n=30 patients post-transplant; of these, 21 SAEs occurred in n=5 patients; n=1 died from intracranial bleeding associated with previous moya disease after relapse of SCD post-transplant Most common SAEs (n= number of SAEs) were: • pain and related management (n=15, eg arthralgias, myalgias, narcotics withdrawal) • infections (n=6), *Clostridium difficile* (n=2),			

[102] A further n=4 SAEs were recorded, of which n=3 were related to femoral catheter placement (all in donors), and n=1 was death from a cardiac cause in a patient with SCD before transplant. Hospitalisations post-transplant were captured through SAE reporting rather than via separate reporting;

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Babesia (n=1), skin abscess (n=1), malaria (n=1), pneumonia (n=1)) • abdominal events (n=6, eg pain ulcer, pancreatitis) • sirolimus-related toxicities (n=5, eg arthralgia, pneumonitis) Other side effects (not reported as SAEs) included: n=3 cases of thyroiditis			
				Primary Safety	Changes in end-organ function (cardiopulmonary)	At baseline, n=13/30 (43%) had tricuspid regurgitant velocity (TRV) >2.5m/s Mean TRV (m/s, 95%CI) pre-transplant 2.84 (2.71-2.99); post-transplant 2.57 (2.44 -2.69) at 1 month (n not stated), 2.43 (2.12-2.70) at 1 year (n not stated), 2.33 (2.14-2.51) at 3 years (n not stated), p = 0.01 for TRV 2.6 - 2.9m/s, p < 0.001 for TRV ≥ 3m/s			

Use of HSCT for adults with SCD (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Mean 6-minute walk test (m, 95%CI): pre-transplant 455 (244 - 665); post-transplant 504 (206 – 801) at 1 year, 507 (332 – 681) at 3 years, p = 0.41			
				Primary Safety	Changes in end-organ function (central nervous system)	No cases of stroke or cerebral bleeding peri-transplant in n=9 patients with history of stroke or abnormal CNS vessels pre-transplant. Subsequent post-transplant annual brain MRI (n not stated): unchanged in patients with sustained engraftment; n=1 patient who relapsed died from recurrent stroke. n=1 patient with history of infrequent complex partial seizure had 2 self-limited episodes at 2 and 3 months post-transplant			
				Primary Safety	Changes in end-organ function (hepatic)	Approximately two-thirds (n not stated) of n=30 patients who received HSCT had variable increases in transaminases and alkaline phosphatase post-transplant; these parameters gradually improved with no			

Use of HSCT for adults with SCD (no comparator)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						specific treatment n=15 had ferritin levels >1000ng/mL at baseline; of these n=9 had liver biopsy; of these n=8 had histology available which showed varying levels of inflammation but no baseline measure was available for comparison			
				Primary Safety	Changes in end-organ function (renal)	n=4 (13%) had sickle nephropathy (serum creatinine ≥ 1.3 mg/dL) pre-transplant; no worsening of previously established decline in renal function was observed post-transplant			
				Primary Safety	Post-HSCT large volume phlebotomy for iron overload	n=13/30 (43%) (of whom n=7 had completed phlebotomy and n=6 continued to undergo phlebotomy by study endpoint)			

Allo-HSCT- allogeneic haematopoeitic stem cell transplantation; Allo-PSCT - allogeneic peripheral blood stem cell transplantation; ATG - anti-T cell lymphocyte globulin; BM - bone marrow; BKV - BK virus; Bu - busulfan; CMV - cytomegalovirus; cGy – centigray (a measurement unit of radiation); CI - confidence intervals; CNS - central nervous system; Cy - cyclophosphamide; EBV - Ebstein-Barr virus; Flu - fludarabine; G-CSF - granulocyte-colony stimulating factor; GI - gastro-instestinal; GvHD - graft versus host disease (aGvHD – acute graft versus host disease; cGvHD - chronic graft versus host disease); Hb and Hgb – haemoglobin; HbS - haemoglobin S; HbSS, HbSC, HbSS, HbS β0 thalassaemia, HbS β+ thalassaemia - genetic variants of sickle cell disease; HCT-CI - Haematopoietic cell transplantation-specific comorbidity index HLA - human leukocyte antigen; HPC - human progenitor cell transplantation; IQR - interquartile range; LVEF - left ventricular ejection fraction; MAC - myeloablative conditioning; nMAC – non-myeloablative conditioning; MRI - magnetic resonance imaging; NIH - National Institutes for Health; RBC - red blood cell; RIC – reduced intensity conditioning; SAE - serious adverse event; SCD - sickle cell disease; SD - standard deviation; SE - standard error; TBI - total-body irradiation; PB - peripheral blood; PT - post-transplantation; SC - sickle cell; SCD - sickle cell disease; SAE – Serious Adverse Event

8 Grade of Evidence Table

For abbreviations see list after each table

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall survival	Ozdogu et al (2018)	5	Direct	B	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). 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 number of patients alive at different time points was not reported. 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.
	Gluckman et al (2017)	7	Direct		
	Fitzhugh et al (2017)	6	Direct		
	Hsieh (2014)	6	Direct		
Event-free survival	Gluckman et al (2017)	7	Direct	B	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). 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. 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 number of patients alive at different time points was not reported.. The retrospective design introduces the possibility of selection bias. Heterogeneity amongst the study population, HSCT donor type and conditioning

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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.
Disease-free survival	Ozdogu et al (2018)	5	Direct	B	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); 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)[103]. 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 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 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 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. Fitzhugh et al (2017) reported higher rates of disease-free survival among patients who received the highest dose of post-transplant cyclophosphamide but it was not clear how patients were initially allocated to the different cyclophosphamide regimens. Since neither study included a comparator, it is not possible to compare the outcomes for these patients with those receiving alternative treatments.
	Fitzhugh et al (2017)	6	Direct		
	Hsieh et al (2014)	6	Direct		
Non-relapse mortality	Ozdogu et al (2018)	5	Direct	B	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.
	Hsieh et al (2017)	6	Direct		

[103] 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

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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.
Engraftment	Ozdogu et al (2018)	5	Direct	B	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[104] 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. Both studies were small uncontrolled prospective studies of HSCT in adults with SCD and/or thalassaemia using non-myeloablative 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.
	Allen et al (2017)	5	Direct		
	Fitzhugh et al (2017)	6	Direct		
	Hsieh et al (2014)	6	Direct		

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

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Graft failure or rejection	Ozdogu et al (2018)	5	Direct	B	Graft failure[105] 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.[106] 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. 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.
	Allen et al (2017)	5	Direct		
	Fitzhugh et al (2017)	6	Direct		
	Hsieh et al (2014)	6	Direct		
Donor chimerism	Ozdogu et al (2018)	5	Direct	**B**	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
	Fitzhugh et al (2017)	6	Direct		
	Hsieh et al (2014)	6	Direct		

[105] The terms graft failure and graft rejection were not defined by included studies and appeared to be used interchangeably by some studies. Graft rejection is a major cause of graft failure and is due to recipient immune response against donor immunohematopoietic cells (Mattsson et al 2008).
[106] One of these patients died from intracranial bleeding associated with previous moyamoya disease after relapse of SCD

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					(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% to100%), 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)[97]). 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. Both studies were small uncontrolled prospective studies of HSCT in adults with SCD and/or thalassaemia using non-myeloablative 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.
Graft versus host disease	Ozdogu et al (2018)	5	Direct	B	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[107]. In the study by Gluckman et al (2017), the risk for acute GvHD[108] 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 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[109] for adult patients aged ≥16 years was 77% (no 95%CI reported).
	Gluckman et al (2017)	7	Direct		
	Fitzhugh et al (2017)	6	Direct		
	Hsieh et al (2014)	6	Direct		

[107] https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf
[108] 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
[109] Defined as the probability of being alive without having experienced either grade III or grade IV aGVHD or extensive cGVHD

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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. 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.
Quality of life (SF-36)	Ozdogu et al (2018)	5	Direct	C	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. 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 the study results. Follow-up for most outcomes, including quality of life, 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.
Transfusion requirement	Allen et al (2017)	5	Direct	B	Transfusion requirement refers to the frequency of red blood cell transfusions received by patients before and after transplantation. In the study by Hsieh et al (2014), pre-transplant, n=16 (53%) patients had simple/exchange
	Hsieh et al (2014)	6	Direct		

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					red blood cell transfusions (number/frequency not stated); post-transplant, one patient[110] (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. 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.
Narcotic use	Ozdogu et al (2018)	5	Direct	B	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. 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.
	Hsieh et al (2014)	6	Direct		

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

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Hospitalisation	Ozdogu et al (2018)	5	Direct	B	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[111] (reported as number of hospitalisations per patient per year) for the year pre-transplant was 3.23[112] (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. 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.
	Hsieh et al (2014)	6	Direct		
Painful crisis	Ozdogu et al (2018)	5	Direct	C	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

[111] 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

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

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					alternative treatments.
Immunosuppression	Ozdogu et al (2018)	5	Direct	B	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[113] (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. 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.
	Fitzhugh et al (2017)	6	Direct		
	Hsieh et al (2014)	6	Direct		
Transplant-related infection	Ozdogu et al (2018)	5	Direct	B	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) 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).
	Fitzhugh et al (2017)	6	Direct		
	Hsieh et al (2014)	6	Direct		

[113] 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%

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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. Both studies were small uncontrolled prospective studies of HSCT in adults with SCD and/or thalassaemia using non-myeloablative 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.
Transplant-related complications (non-infectious)	Ozdogu et al (2018)	5	Direct	B	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) eg 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. Both studies were small uncontrolled prospective studies of HSCT in adults with SCD and/or thalassaemia using non-myeloablative 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
	Allen et al (2017)	5	Direct		
	Fitzhugh et al (2017)	6	Direct		
	Hsieh et al (2014)	6	Direct		

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					these patients with those receiving alternative treatments.
Changes in end-organ function - renal	Hsieh et al (2014)	6	Direct	C	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. 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.
Changes in end-organ function - cardiopulmonary	Hsieh et al (2014)	6	Direct	C	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. 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

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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.
Changes in end-organ function central nervous system	Hsieh et al (2014)	6	Direct	C	Complications of SCD include stroke, cerebral haemorrhage and epilepsy. Hseih 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. 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.
Changes in end-organ function - hepatic	Ozdogu et al (2018)	5	Direct	B	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 Hseih 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 Hseih et al 2014 were the result of the transplants, and what effect they had on patients. 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.
	Hsieh et al (2014)	6	Direct		
Large volume phlebotomy for iron	Hsieh et al (2014)	6	Direct	C	Large volume phlebotomy is the treatment for iron overload which is a complication of HSCT.

Use of HSCT for adults with SCD (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
overload					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. 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.

9 Literature Search Terms

Search strategy Indicate all terms used in the search	
P – Population and Indication Define the patient group and indication that is the focus of the evidence review, and the point in the care pathway that needs to be addressed? Specific subgroups of interest should be identified if there is a related research question114.	Adult patients (aged 18 years and older) with SCD (All genotypes)
I – Intervention Which intervention, treatment or approach should be used? If it is a device or a pharmacological intervention, please use the generic name. Confirm if the intervention is used as monotherapy. If not, specify the concomitant treatments.	Haematopoietic Stem Cell Transplantation (Bone Marrow Transplantation)
C – Comparison What is/are the main alternative treatment/s relevant to UK clinical practice to compare with the intervention being considered?	Standard care, (which may include red-cell blood transfusion and/or hydroxycarbamide / hydroxyurea)
O – Outcomes What is really important for the patient? Which outcomes should be considered? E.g. Clinical effectiveness: mortality, morbidity, adverse effects; treatment complications, relapse, re-admission quality of life; activities of daily living, return to work, physical and social functioning, Cost effectiveness Resource utilisation Cost per QALY	Critical to decision-making: Survival (including transplant-related mortality) Acute health events Number of acute sickle cell disease complications (e.g. pain, stroke, acute chest syndrome) Acute hospital utilisation due to SCD or problems secondary to SCD Chronic health outcomes e.g. neurological complications, pulmonary hypertension, renal complications, hepatic complications, ophthalmologic complications Transfusion independence (freedom from transfusions) Important to decision-making: Quality of life Including measures of psychological health Adverse events Rate of failure or rejection of HSCT Rate of Graft versus Host Disease

[114] Note: The rapid evidence review methodology does not support separate searches for subgroups, unless commissioned to undertake separate reviews for these specific populations.

	Number or rate of infections post-transplant Cost-effectiveness
Assumptions / limits applied to search The search for peer reviewed published evidence will be conducted by applying relevant subject headings, free text terms and study type filters where appropriate to bibliographic databases according to using the criteria specified in this PICO table. Standard exclusion criteria will usually be applied unless otherwise discussed and approved with NHS England Clinical Effectiveness Team. Exclusion criteria: Studies which are not able to be identified and retrieved via one of the following search engines: MEDLINE, Embase and the Cochrane Library Studies published in languages other than English Studies published more than 10 years ago Grey literature including conference papers, abstracts, posters, letters, internet publications and manufacturer documents Consider controlled studies, uncontrolled studies and case series	

10 Search Strategy

We searched Medline, Embase and Cochrane Library limiting the search to papers published in England from 1st January 2008 to 16th August 2018. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 16th August 2018
Embase search:

# ▲	Searches
1	exp sickle cell anemia/
2	sickle cell.ti,ab.
3	1 or 2
4	hematopoietic stem cell transplantation/ or *stem cell transplantation/ or allogeneic hematopoietic stem cell transplantation/ or autologous hematopoietic stem cell transplantation/
5	*bone marrow transplantation/
6	((H?ematopoietic or Stem Cell or bone marrow or allo* or auto*) adj3 (transplant* or allotransplant*)).ti,ab.
7	(hct or hsct or allohct or allohsct or autohct or autohsct or bmt).ti,ab.
8	4 or 5 or 6 or 7
9	3 and 8
10	limit 9 to (english language and yr="2008 - Current")
11	conference*.pt.
12	10 not 11

11 Evidence Selection

- Total number of publications reviewed: 46
- Total number of publications considered potentially relevant: 13
- Total number of publications selected for inclusion in this briefing: 5

References from the PWG supplied in the PPP		Paper selection decision and rationale if excluded
1.	Hsieh M. Fitzhugh C. Weitzel R. Link M. Coles W. Zhao X. Rodgers G. Powell J. Tisdale J. 2014. Nonmyeloablative HLA-Matched Sibling Allogeneic Hematopoietic Stem Cell Transplantation for Severe Sickle Cell Phenotype. *JAMA, 312(1):48.*	Included
2.	Gluckman E. Cappelli B. Bernaudin F. Labopin M. Volt F. Carreras J. Pinto Simões B. Ferster A. Dupont S. de la Fuente J. Dalle J. Zecca M. Walters M. Krishnamurti L. Bhatia M. Leung K. Yanik G. Kurtzberg J. Dhedin N. Kuentz M. Michel G. Apperley J. Lutz P. Neven B. Bertrand Y. Vannier J. Ayas M. Cavazzana M. Matthes-Martin S. Rocha V. Elayoubi H. Kenzey C. Bader P. Locatelli F. Ruggeri A. Eapen M. 2016. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. *Blood, 129(11):1548-1556.*	Included
3.	-Not supplied	-

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