MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
29 05 2019 and 30 05 2019

Agenda Item No	02.2
National Programme	Blood and Infection
Clinical Reference Group	Blood & Marrow transplant
URN	1742

Title
Allogeneic haematopoietic stem cell transplant (HSCT) for primary immunodeficiencies (PID) (all ages)

Actions Requested	1. Support the policy proposition
	2. Recommend for in year service development

Proposition
Routinely Commissioned. Allo-HSCT replaces the patient's own bone marrow stem cells with healthy stem cells from a donor. If successful, this cures the PID. The decision to treat a patient with allo-HSCT is made on an individual basis, depending upon the type and severity of the immune deficiency. Allo-HSCT is not a new treatment in children with PID, and for some adults the treatment is currently commissioned under the Urgent Clinical Commissioning Policy Statement: Allogeneic stem cell transplantation for adults with Primary Immune Deficiency disorders, which this policy will replace. This policy document covers all ages.

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

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes / Head of Mental Health Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment

	Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

1a Allo-HSCT for PID – ALL AGES – no comparator		
No	Metric	Summary from evidence review
1.	Survival	Fixed-term survival is the proportion of patients alive at a specified interval. In Mitchell et al (2013), 5-year survival was 72% (confidence intervals (CI) not reported). In multivariate analysis, decreased survival was significantly associated with active CMV, interstitial pneumonitis and veno-occlusive disease ($p<0.05$). 5-year survival for the most common PIDs was 70% for Severe combined immunodeficiency (SCID), 81% for WAS and 69% for Chronic granulomatous disease (CGD). A high overall survival rate in the context of a life-threatening condition is a positive outcome. However, a longer median follow-up would give better evidence about the impact on survival. This study included any PID. Median age at HSCT was 1 year (range 0-15); median follow-up was 6 years (range 0.39 to 17.31). This uncontrolled retrospective review included patients from 6 centres in Australia and New Zealand treated over 17 years to 2008 and had a moderate sample size (n=135). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	Karnofsky/ Lansky scores determine functional status. The Karnofsky Scale is for people aged ≥16 years; the Lansky Scale is for people <16 years. Both are scored from 10 to 100. Higher scores indicate better function[1]. In de la Morena et al (2017) surviving patients treated with HSCT had higher median scores (100%) than patients who did not receive HSCT (90%) at last follow-up ($p<0.001$). A score of 100% is defined as “normal, no complaints, no evidence of disease” on the Karnofsky Scale and “fully active” on the Lansky Scale. A score of 90% is defined as “able to carry on normal activity” on the Karnofsky Scale and “minor restriction in physically strenuous play” on the Lansky Scale. This study included X-linked hyper Immunoglobulin M (IgM) syndrome patients. Mean follow-up was 8.5±7.2 years. Median age at HSCT was 2.9 years (range 0.1 to 24). This uncontrolled retrospective review included patients treated at 28 centres worldwide over 49 years to 2013 and had a moderate sample size (n=176). Although results are presented for patients who did and did not receive HSCT it is not a comparative study. Reasons why patients did not

		receive HSCT are not reported. The retrospective design and lack of controlled comparator limit the strength of the conclusions that can be drawn.
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	Safety outcomes include cause of death, adverse events and Graft versus Host Disease(GvHD). In GvHD the donated cells react against the patient's body which can lead to an immune response attack. GvHD is graded as I–mild; II–moderate; III–severe; IV–life threatening. In Mitchell et al (2013), 36 patients (27%) died. Cause of death included infection (22%), interstitial pneumonitis (non-infectious) (17%), GvHD (14%), graft failure (14%), organ failure (14%), haemorrhage (11%) and acute respiratory syndrome (non-infectious) (8%). Adverse events after HSCT included Cytomegalovirus (CMV) (19%), interstitial pneumonitis (15%), veno-occlusive disease (13%) and haemorrhagic cystitis (4%). 100 day cumulative incidence for acute GvHD (grade II to IV) was 25%. 1-year cumulative incidence for chronic GvHD was 16%. In multivariate analysis decreased risk of GvHD was significantly associated with the use of a fully matched sibling donor and HSCT performed after 1998 (p=0.002). The number of deaths and adverse events reported reflects the seriousness of PID and risks associated with HSCT. See above for details and limitations of Mitchell et al.
11.	Delivery of intervention	

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report

[1] Center for International Blood & Marrow Transplant Research 2009

3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

CGD-chronic granulomatous disease; CI–confidence intervals; CMV – cytomegalovirus; GvHD-graft-versus-host disease; IgM-Immunoglobulin M; SCID-severe combined immune deficiency; WAS-Wiskott-Aldrich syndrome

1b Allo-HSCT for PID – ALL AGES – no comparator		
No	Metric	Summary from evidence review
1.	Overall survival	Overall survival is the proportion of patients alive at last follow-up. In Moratto et al (2011), overall survival was 82% (CI not reported). In multivariate analysis, better survival was associated with HSCT after the year 2000 ($p<0.05$) and reduced survival was associated with use of a mismatched[2] family donor or cord blood ($p<0.05$). A high overall survival rate in the context of a life-threatening condition is a positive outcome. However, a longer median follow-up period would give better evidence about the impact on survival. This study included Wiskott-Aldrich syndrome (WAS) patients. Median age at HSCT was 34.6 months (range 2 to 240); median follow-up was 76.8 months (range 12 to 346). This uncontrolled retrospective review included patients from 12 European and American centres treated over 29 years to 2009 and had a moderate sample size (n=194). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
2.	Long-term survival >2 years after HSCT	Long term survival is the proportion of patients who survived >2 years after HSCT who were still alive at last follow-up. In Eapen et al (2012), 7-year long-term survival was 93% (95%CI 89 to 97) for SCID patients and 96% (95%CI 94 to 98) for non-SCID patients. 9-year survival was 92% for SCID and 96% for non-SCID (CI not reported). The high survival rates suggest that most patients who survive the first 2 years after HSCT have a positive survival outcome. A longer median follow-up period would give better evidence about the impact on survival.

[2] Mismatched donors are used when a matched donor is not available and do not have human leukocyte antigens that are identical to the patient

		Median age at HSCT was not reported; 97% of SCID and 63% of non-SCID were <2 years old. Median follow-up was 7.8 years for SCID and 6.3 years for non-SCID. This uncontrolled retrospective review included patients from 114 worldwide centres treated over 23 years to 2003 and had a large sample (n=606). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
3.	Transplant-related mortality(TRM)	TRM was defined as death from any cause other than persistent disease. In Mitchell et al (2013) cumulative incidence of TRM at 100 days was 10%. At 1-year this was 22%. In multivariate analysis, increased risk of TRM was significantly associated with active CMV, interstitial pneumonitis and veno-occlusive disease. The TRM rate of 22% at 1-year reflects the seriousness of PID and the risks associated with HSCT. See above for details and limitations of Mitchell et al.
4.	Relative mortality rate	Relative mortality is the relative risk of dying at a given time after transplantation as compared with a person of similar age, sex, and nationality in the general population. In Eapen et al (2012) excess deaths per 1,000 compared to an age, sex and nationality matched population was 54 (95%CI 28 to 79) for SCID and 38 (95%CI 25 to 51) for non-SCID for 2-6 years after HSCT. In 6-10 years after HSCT there was no significant difference in mortality risks for surviving patients compared to the general population. The lack of difference in mortality risk compared to the general population beyond 6 years suggests long term outcomes for patients who survive the first few years after HSCT are positive, although it may also reflect the smaller number of patients for whom longer term data are available. See above for details and limitations of Eapen et al.
5.	Engraftment	Engraftment occurs when the stem cells of the donor have been taken up by the patient's bone marrow and produce new blood and immune system cells. Neutrophil engraftment was defined as the first of 3 consecutive days of absolute neutrophil count of $\geq 0.5 \times 10^9$/L and platelet engraftment was defined as a platelet count of $\geq 20 \times 10^9$/L measured a minimum of 7 days after the last platelet transfusion.

		In Mitchell et al (2013), neutrophil engraftment was 89% with median time to engraftment 16 days (range 1-62) and platelet engraftment was 85% with median time to engraftment 30 days (range 1-112). High levels of engraftment are a positive outcome for HSCT, indicating successful uptake of donor cells. See above for details and limitations of Mitchell et al.
6.	Immunologic response	Immunologic reconstitution outcomes include the normalisation of T and B lymphocytes and T lymphocyte subsets ($CD3^+$>1,000, $CD4^+$>600, $CD8^+$>300, $CD19^+$>200 cells/µL) and the requirement for IVIG after HSCT. Moratto et al (2011) reported immunologic reconstitution ≥12 months after HSCT. 68% showed normalisation of the absolute count of T and B lymphocytes and of T lymphocyte subsets and 13% required IVIG. A majority of patients achieved normalisation, but some still required IVIG. See above for details and limitations of Moratto et al.
7.	Chimerism	Chimerism relates to the presence of donor cells after transplantation. Mixed chimerism is a combination of patient and donor cells. In full chimerism only donor cells are present. Low chimerism was 5% to 50% of donor cells. Null chimerism was <5% donor cells. In Moratto et al (2011), 28% showed mixed chimerism in ≥1 of the cell lineages tested (T lymphocytes, B lymphocytes, myeloid cells). Low or null donor chimerism was more common within myeloid cells (16.5%) than in B lymphocytes (7.4%) or T lymphocytes (3.2%). Mixed chimerism after HSCT for WAS has been reported to be associated with increased risk of autoimmunity[3]. See above for details and limitations of Moratto et al.
8.	Requirement for more than one HSCT	Further transplantation can be required due to graft failure or rejection. In Mitchell et al (2013) 18 (13%) patients required a 2nd HSCT. A relatively low proportion of patients required a 2nd HSCT.

[3] An immune response against a person's own healthy cells and tissues

		See above for details and limitations of Mitchell et al.
9.	Admission to intensive care	Complications after HSCT can lead to admission to paediatric or adult Intensive Care Unit (ICU) where support can be provided for failing organ systems such as ventilation, cardiovascular support and renal replacement therapy. In Cole et al (2012), 35% required at least one ICU admission at a median of 31 days after HSCT for the 1st admission (range -6 to 834). The most common reason for admission was respiratory problems (59%). Other reasons included surgical problems (17%), complications related to veno-occlusive disease (9%), cardiovascular instability (5%), infection (5%) and neurological problems (5%). Median admission duration was 6 days (range 1-35). That more than a third of patients required an ICU admission reflects the serious, life-threatening nature of PID and the risks associated with HSCT. This study included patients with any PID. Median age at HSCT was 1 year 4 months (range 1 month to 19 years). Follow-up period not reported. This uncontrolled retrospective review included patients treated at 1 UK centre over 5 years to 2009 and had a moderate sample size (n=111). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
10.	Post-transplant malignancy	Post-transplant malignancy was defined as the development of a new malignancy after HSCT. Only cases confirmed by pathology reports and/or confirmed with the transplant centre were included. In Kamani et al (2011), 52 (2.3%) developed a confirmed post-transplant malignancy, of whom 40 had died at follow-up. Cumulative incidence of malignancy was 2% (95%CI 2 to 3) at 5-years; 2% (95%CI 2 to 3) at 10-years and 3% (95%CI 2 to 5) at 15 years. Cumulative incidence was higher in WAS patients (4%, 95%CI 2 to 6 at 5, 10 and 15 years) than SCID patients (2%; 95%CI 1 to 3 at 5 and 10 years and 3%; 95%CI 1 to 6 at 15 years). Lymphoproliferative disorders were the most common malignancy, occurring in 45 patients (87%) with a median time to development of 3 months after HSCT (range 1-41). Kamani et al report that the overall risk of cancer in children with PID is estimated to be 4%. This study included patients with any PID. Median age at HSCT was 1 year (range 1.2 months to 47 years); median follow-up was 6 years (range 4 to 14). This uncontrolled retrospective review included patients treated at over 500

		centres worldwide over 35 years to 2003 and had a large sample size (n=2,266). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
11.	Quality of life	Quality of life was assessed using a non-validated SCID-specific questionnaire developed by the study authors and sent to families of 111 surviving patients during study follow-up (timings not reported). In Railey et al (2009) 86% of patients were considered to be healthy by their families, with 36% reporting no health problems in the last 2 years. The most commonly reported health problems (affecting ≥10%) were persistent rash (25%), sinusitis (20%), asthma (14%), diarrhoea (14%), ADHD (21%) and developmental delay (10%). 12% of patients were below the 3rd percentile for height and weight and 3% required special schooling. A high proportion of the surviving patients were considered healthy by their families. This study included SCID patients who did not receive pre-transplant chemotherapy or post-transplant GvHD prophylaxis and had a median follow-up of 8.7 years (range 2.9 to 14.1). Age at HSCT not reported. This uncontrolled retrospective review included patients treated at 1 US centre over a 16 year period to 2008, and had a moderate sample size (n= 161). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
12.	Centre assessment	Centres' assessment of post-HSCT outcome for surviving patients related to the underlying WAS disease was assessed although no definitions for the categories used were reported. In Filipovitch et al (2001) 53% of patients were considered 'cured', 18% 'improved', 3% 'unchanged' and 3% 'worse'. Status was not reported for 23%. 71% of the 120 surviving patients were considered 'cured' or 'improved'. However, data was missing for 23% of surviving patients. This study included Wiskott-Aldrich syndrome (WAS) patients. Median follow-up was 42 months (range 2 to 304). This uncontrolled retrospective review included patients treated at 60 worldwide centres over a 28 year period to 1996, and had a moderate sample size (n=170). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.

ADHD-attention deficit hyperactivity disorder; CI–confidence intervals; CMV – cytomegalovirus; GvHD -graft-versus-host disease; ICU-intensive care unit; IVIG - intravenous immunoglobulin; SCID-severe combined immune deficiency; TRM – transplant-related mortality; WAS-Wiskott-Aldrich syndrome

2a Allo-HSCT for PID – ADULTS – no comparator		
No	Metric	Summary from evidence review
1.	Survival	Overall survival is the time from transplant to death from any cause. In Fox et al (2018), overall survival was 89% at 1 year and 85% at 3 years (CI not reported) in adults with a variety of PIDs who had developed complications that necessitated definitive treatment with curative intent (i.e. HSCT). A high overall survival rate is important to clinicians, patients and their families. This small, uncontrolled retrospective study included 29 patients who received HSCT at 2 UK centres over 12 years to 2016. The study does not include a comparison with any alternative treatment strategy. Mean follow-up was relatively short at 3.5 years and no confidence intervals were reported so the precision of the result is unclear. The retrospective design introduces the possibility of selection bias and the lack of comparator limits the strength of the conclusions that can be drawn.
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	See below.
11.	Delivery of intervention	

2b Allo-HSCT for PID – ADULTS – no comparator

No	Metric	Summary from evidence review
1.	Event-free survival	Event-free survival is the time from transplant to graft failure, graft rejection or death from any cause. In Fox et al (2018) event-free survival was 90% at 1 and 3 years (CI not reported) in adults with a variety of PIDs who had developed complications that necessitated definitive treatment with curative intent (i.e. HSCT). A high event-free survival rate is important to clinicians, patients and their families. See above for details and limitations of Fox et al.
2.	Post-transplant infection	Post-transplant infection relates to the infections experienced by patients after transplantation. In Fox et al (2018) 69% of patients had infections post-transplant. Infections experienced by more than one patient included CMV reactivation, EBV reactivation, sepsis, warts and human papillomavirus. A high proportion of patients experienced post-transplant infections. Infections after transplantation can be life threatening. No grading system was used to specify the seriousness of the infections reported so the clinical meaningfulness is unclear. See above for details and limitations of Fox et al.
3.	Engraftment	Engraftment occurs when donor stem cells have been taken up by the patient's bone marrow and produce new blood and immune system cells. Engraftment outcomes include: graft failures or rejections[4]; time to neutrophil engraftment (defined as ≥0.5 x 10^9/L) and time to platelet engraftment (defined as ≥50 x 10^9/L). In Fox et al (2018) there were no graft failures or rejections. Median time to neutrophil engraftment was 12 days (IQR 11 to 17) and median time to platelet engraftment was 14 days (IQR 11 to 20). Engraftment is a positive outcome implying that the patient is successfully producing new blood and immune cells. See above for details and limitations of Fox et al.
4.	Chimerism	Chimerism relates to the presence of donor cells after transplantation. Fox et al (2018) defined full donor chimerism as ≥97% donor DNA. Mixed chimerism is a combination of patient and donor DNA. Chimerism is often reported by

[4] Not further defined

		specific lineages i.e. for peripheral blood mononuclear cells, T-cells, B-cells and granulocyte compartments or across multiple lineages. In Fox et al (2018), 48% of 21 surviving patients had achieved multi-lineage full donor chimerism at 12 months. The proportion of patients achieving full donor chimerism for specific lineages was 85% for unfractionated peripheral blood mononuclear cells, 52% for T-cells, 69% for B-cells and 67% for granulocytes. Full donor chimerism is a positive outcome. The study authors (Fox et al 2018) indicated that the degree of donor chimerism required to achieve a functional cure is not known for all PIDs. See above for details and limitations of Fox et al.
5.	Immune reconstitution	Immune reconstitution relates to the recovery of the immune system. Outcomes included continued requirement for monthly immune replacement and receipt of immunosuppression post-transplant. In Fox et al (2018) monthly immune replacement had ceased in 89% of 9 patients who had been receiving replacement pre-transplant. 76% of 29 patients were not receiving immunosuppression at last follow-up. Immune reconstitution is a positive outcome, implying recovery of the immune system which is likely to have a positive impact on quality of life. See above for details and limitations of Fox et al.
6.	Transplant-related mortality	TRM is death from cause related to the transplant. In Fox et al (2018) TRM was 14% (4 patients). Cause of death for 2 patients was multi-organ failure secondary to sepsis and cause of death for the other 2 patients was granulomatous meningoencephalitis and sepsis in the context of extensive chronic GvHD. The number of transplant-related deaths was considered low by the study authors, reflecting the seriousness of PID and the risks associated with HSCT. A low TRM rate is important to clinicians, patients and their families. See above for details and limitations of Fox et al.
7.	Graft-versus-host disease	In GvHD 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 100 days after transplant. Acute GvDH is graded as I=mild;

		II=moderate; III=severe; and IV=very severe. Chronic GvHD is generally graded as mild, moderate or severe[5]. In Fox et al (2018), 45% of 29 patients had acute GvHD. This was 28% with mild disease, 14% with moderate disease and 3% with severe disease. There were no cases of very severe acute GvHD. 28% of 29 patients had chronic GvHD. Grading for chronic GvHD was not reported, but this included 7 patients (24%) who had progressed from acute GvHD and 1 patient (3%) who had steroid refractory extensive chronic GvHD. GvHD is an adverse outcome of HSCT and in severe cases can be life-threatening. The majority of cases reported were mild to moderate. See above for details and limitations of Fox et al.
8.	Transplant-related complications (non-infectious)	Transplant-related complications relates to non-infectious complications after transplant. In Fox et al (2018) 69% of 29 patients had post-transplant complications. Complications experienced by >1 patient included requirement for donor lymphocyte infusions, multi-organ failure, EBV post-transplant lymphoproliferative disease, renal impairment and prolonged cytopenias. A high proportion of patients experienced post-transplant complications. Complications after transplant can be life threatening. No grading system was used to specify seriousness so the clinical meaningfulness is unclear. See above for details and limitations of Fox et al.

CI–confidence intervals; CMV–cytomegalovirus; EBV–Epstein Barr virus; GvHD - graft-versus-host disease; TRM– transplant-related mortality

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
The proposal received the full support of the Blood and Infection PoC on the 28th February 2019.

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