CLINICAL PRIORITIES ADVISORY GROUP
10 07 2023

Agenda Item No	
National Programme	Blood and Infection
Clinical Reference Group	Immunology and Allergy
URN	2120

Title
Allogeneic Haematopoietic Stem Cell Transplantation (Allo-HSCT) for adult transfusion dependent thalassaemia

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation

Proposition
For routine commissioning This is a clinical commissioning policy proposition for the use of allo-HSCT is recommended to be available as a routine commissioning treatment option for adults with transfusion dependent thalassaemia (TDT). The proposition is restricted to adults as allo-HSCT is already commissioned for a number of disorders including children aged up to 18 years with TDT. Allo-HSCT is also known as bone marrow transplantation (BMT). It is a curative intervention already used to treat a wide spectrum of disorders, including children with TDT up to the age of 18 years. Transplantation involves replacing the bone marrow stem cells of a patient with stem cells from a donor. Haematopoietic stem cells are found in bone marrow and blood in adults. They are delivered to a patient through intravenous infusion, to re-establish blood cell production in patients whose bone marrow or immune system is damaged or defective.

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

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

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

In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Outcome 1 **Overall survival** **Certainty of evidence:** Very low	This outcome is important to patients because it reflects how long people live after transplant, although it does not provide information about patients' health and wellbeing during that time. In total, 3 studies (1 retrospective case control study and 2 retrospective case series) provided evidence relating to overall survival measured at different time points (2 years, 5 years and 23 years). All included children in the total population but presented subgroup analyses in adults. In the case control study (Caocci et al. 2017), 97 adults aged 16 years or older (median age 23 years) who had allogenic HSCT were matched according to age and sex with 97 adults who had standard treatment. The case series were uncontrolled registry studies, which included

	people who had allogenic HSCT. One case series (Baronciani et al. 2016) included 133 adults aged 18 years or older (median age 22.9 years), but survival data are reported only for 82 adults (62%) who had an HLA-identical sibling donor. The other case series (Li et al. 2019) included 33 adults aged 16 to 25 years (median age of subgroup not reported). ***Allogenic HSCT compared with standard treatment*** In the case control study (Caocci et al. 2017), there was no difference in overall survival in adults who had HSCT (n=97) or standard treatment with blood transfusions and iron chelation (n=97). After 23 years, the probability of overall survival was 70.0% in the HSCT group compared with 71.2% in the standard treatment group (no statistically significant difference, p value not reported). **(VERY LOW)** ***Allogenic HSCT (no comparator)*** In the first case series (Baronciani et al. 2016, n=82), 2-year overall survival was 80% in the adult subgroup. **(VERY LOW)** In the second case series (Li et al. 2019, n=33), 5-year overall survival was 63% (95% CI 45% to 82%) in the adult subgroup after adjusting for donor type and conditioning regimen. **(VERY LOW)** **One case control study provided very low certainty evidence that overall survival rates are similar in adults with TDT who have allogenic HSCT or standard treatment, with about 7 out of 10 people surviving at 23 years in each group. Two case series provided very low certainty evidence that 8 out of 10 adults with TDT who have allogenic HSCT survive after 2 years and 6 out of 10 adults survive after 5 years.**
Outcome 2 **Event free survival** **Certainty of evidence:** Very Low	This outcome is important to patients because it reflects how long people live after transplant until either death or thalassaemia recurrence. In total, 3 studies (1 retrospective case control study and 2 retrospective case series) provided evidence relating to overall survival measured at different time points (2 years, 5 years and 23 years). All included children in the total population but presented subgroup analyses in adults. In the case control study (Caocci et al. 2017), 97 adults aged 16 years or older (median age 23 years) who had allogenic HSCT were matched according to age and sex with 97 adults who had standard treatment. The case series were uncontrolled registry studies, which included people who had allogenic HSCT. One case series (Baronciani et al. 2016) included 133 adults aged 18 years or older (median age 22.9 years), but survival

	data are reported only for 82 adults (62%) who had an HLA-identical sibling donor. The other case series (Li et al. 2019) included 33 adults aged 16 to 25 years (median age of subgroup not reported). ***Allogenic HSCT (no comparator)*** In the case control study (Caocci et al. 2017), no data were reported for event free survival in adults who had standard treatment. After 23 years, the probability of event free survival was 67.3% in adults who had HSCT (n=97). **(VERY LOW)** In the first case series (Baronciani et al. 2016, n=82), 2-year event free survival was 76% in the adult subgroup. **(VERY LOW)** In the second case series (Li et al. 2019, n=33), 5-year event free survival was 63% (95% CI 48% to 78%) in the adult subgroup after adjusting for donor type and conditioning regimen. **(VERY LOW)** **One case control study and 2 case series provided very low certainty evidence that 6 or 7 out of 10 adults with TDT who have allogenic HSCT survive free of thalassaemia for up to 23 years.**
Outcome 3 **Quality of life** **Certainty of evidence: Very Low**	This outcome is important to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Quality of life can inform the patient centred shared decision making and health policy. One retrospective cross-sectional study (Uygun et al. 2012) provided evidence relating to quality of life in people with TDT who had allogenic HSCT at least 2 years previously (n=49) or standard treatment (n=50). The study included 21 adults aged over 18 years (median age of subgroup not reported) and used the WHOQoL-BREF the questionnaire to assess their health and well-being over the previous 2 weeks. On this questionnaire, higher scores indicate better quality of life. ***Allogenic HSCT compared with standard treatment*** In the cross-sectional study (Uygun et al. 2012), few significant differences were found between HSCT (n=9) and standard treatment with blood transfusions and iron chelation (n=12). The mean quality of life score for the physical domain of the questionnaire was significantly higher in the HSCT group compared with the standard treatment group (79.7 vs 66.6, p=0.041), as was perception of overall health was (80.6 vs 60.4, p=0.034). 'Drug independence for a functional life' and sleep satisfaction were significantly better in the HSCT group compared with the standard treatment group (91.7 vs

	31.3, p=0.001, and 86.1 vs 68.8, p=0.023, respectively). There was no difference between the groups in the total score (78.2 with HSCT vs 72.7 with standard treatment, p=0.181). **One cross-sectional study provided very low certainty evidence that adults with TDT who had allogenic HSCT at least 2 years previously rate their overall health, physical health, sleep and 'drug independence for a functional life' significantly better than adults who have regular blood transfusions and iron chelation. However, there may be little or no difference between the treatments for other quality of life outcomes.**
Important outcomes	
Outcome 4 **Red blood cell transfusion requirement** **Certainty of evidence:** **Not applicable**	This outcome is important to patients because the intention of allogenic HSCT is to replace the need for ongoing transfusion therapy which has major implications on the quality of life and psychological health of patients. A requirement for red blood cell transfusion may also be an indicator of graft failure. **No evidence was identified for this outcome.**
Outcome 5 **Time to donor haematological reconstitution** **Certainty of evidence:** Very Low	This outcome is important to patients because of its significance for the recovery and long-term survival after allogenic HSCT. Reconstitution of the donor-derived immune system is important for control of infectious complications, susceptibility to GVHD and relapse. **No evidence was identified for this outcome.**
Hospitalisation due to TDT or problems secondary to TDT **Certainty of evidence:** **Not applicable**	This outcome is important to patients because frequent hospital attendances can have a negative impact on the psychological health of patients. **No evidence was identified for this outcome.**
Safety	
Outcome 1 **Acute GVHD**	GVHD is a possible complication of allogenic HSCT that occurs when the donor's stem cells (the graft) react against the recipient's (host's) body. Acute GVHD usually develops within the first 100 days after transplant. GVHD is important to patients because it can sometimes be severe and life threatening.

Certainty of evidence: Very low	In total, 3 studies (1 retrospective case control study and 2 retrospective case series) provided evidence relating to acute GVHD. All included children in the total population but presented subgroup analyses in adults. In the case control study (Caocci et al. 2017), 97 adults aged 16 years or older (median age 23 years) who had allogenic HSCT were matched according to age and sex with 97 adults who had standard treatment. The case series were uncontrolled registry studies, which included people who had allogenic HSCT. One case series (Baronciani et al. 2016) included 133 adults aged 18 years or older (median age 22.9 years) and the other (Li et al. 2019) included 33 adults aged 16 to 25 years (median age of subgroup not reported). ***Allogenic HSCT (no comparator)*** In the case control study (Caocci et al. 2017), no data were reported for acute GVHD in adults who had standard treatment (who would not be expected to experience transplant-related adverse events). After 100 days, 26.7% of adults who had HSCT (n=97) had acute GVHD of any severity and 11.6% had severe (grade 3 or 4) acute GVHD. **(VERY LOW)** In the first case series (Baronciani et al. 2016), GVHD was not assessed in the adult subgroup. However, the risk of developing severe (grade 3 or 4) acute GVHD within 100 days of HSCT was 9% in the whole population (n=1223) and the study authors stated that no significant effect of age on acute GVHD was observed. **(VERY LOW)** In the second case series (Li et al. 2019, n=33), 30% of adults had acute GVHD. **(VERY LOW)** **One case control study and 2 case series provided very low certainty evidence that about 3 out of 10 adults with TDT who have allogenic HSCT will experience acute GVHD, and it will be severe in 1 out of 10 adults.**
Chronic GVHD **Certainty of evidence:** **Very low**	GVHD is a possible complication of allogenic HSCT, which occurs when the donor's stem cells (the graft) react against the recipient's (host's) body. Chronic GVHD can develop a few months after the transplant or be a progression of acute GVHD. GVHD is important to patients because it can sometimes be severe and life threatening. In total, 2 studies (1 retrospective case control study and 1 retrospective case series) provided evidence relating to acute GVHD. Both included children in the total

	population but presented subgroup analyses in adults. In the case control study (Caocci et al. 2017), 97 adults aged 16 years or older (median age 23 years) who had allogenic HSCT were matched according to age and sex with 97 adults who had standard treatment. The case series (Baronciani et al. 2016) was an uncontrolled registry study in people who had allogenic HSCT including 133 adults aged 18 years or older (median age 22.9 years). ***Allogenic HSCT (no comparator)*** In the case control study (Caocci et al. 2017), no data were reported for chronic GVHD in adults who had standard treatment (who would not be expected to experience transplant-related adverse events). Of 84 adults who had HSCT and were considered to be at risk, 12.2% had chronic GVHD (median follow up 14 years). **(VERY LOW)** In the case series (Baronciani et al. 2016), GVHD was not assessed in the adult subgroup. However, risk of developing limited chronic or extended chronic GVHD (no definition provided) after 2 years was 15% and 6% respectively in people who survived with a functioning graft for more than 100 days (n=1140) and the study authors stated that no significant effect of age on chronic GVHD was observed. **(VERY LOW)** **One case control study and 1 case series provided very low certainty evidence that about 1 out of 10 adults with TDT who have allogenic HSCT will experience chronic GVHD.**
Graft rejection or failure **Certainty of evidence:** **Very low**	Graft rejection or failure occurs when the transplanted stem cells fail to function by producing new cells. This may be because they fail to attach to the hosts bone marrow and grow or because the host's immune cells reject the donor stem cells. It is important to patients because it can be severe and life threatening. In total, 2 studies (1 retrospective case control study and 1 retrospective case series) provided evidence relating to graft rejection or failure. Both included children in the total population but presented subgroup analyses in adults. In the case control study (Caocci et al. 2017), 97 adults aged 16 years or older (median age 23 years) who had allogenic HSCT were matched according to age and sex with 97 adults who had standard treatment. The case series ((Li et al. 2019) was an uncontrolled registry study in people who had allogenic HSCT including 33 adults

	aged 16 to 25 years (median age of subgroup not reported). ***Allogenic HSCT (no comparator)*** In the case control study (Caocci et al. 2017), no data were reported for chronic GVHD in adults who had standard treatment (who would not be expected to experience transplant-related adverse events). Of 84 adults who had HSCT and were considered to be at risk, 4.7% had graft rejection (median follow up 14 years). **(VERY LOW)** In the case series (Li et al. 2019, n=33), 21% of adults had graft failure. **(VERY LOW)** **One case control study provided very low certainty evidence that about 5 out of 100 adults with TDT who have allogenic HSCT will experience graft rejection. One case series provided very low certainty evidence that about 20 out of 100 adults with TDT who have allogenic HSCT will experience graft failure.**

In the Population what is the cost effectiveness of the Intervention compared with Comparator?

Outcome	Evidence statement
	No evidence was identified regarding the cost effectiveness of allogenic HSCT for adults with TDT compared with standard care.

From the evidence selected, are there any subgroups of patients that may benefit from the intervention more than the wider population of interest?

Outcome:	Evidence statement
Subgroup: age	One case series (Baronciani et al. 2016) found that 2-year overall survival and event free survival significantly decreased with increasing age in the total study population (n=1493, both p<0.001). The case series by Baronciani et al. found age had no significant effect on the rate of acute or chronic GVHD. However, the second case series (Li et al. 2019) found adults aged 16 to 25 years (n=33) were at significantly higher risk of acute GVHD than children aged under 7 years (p=0.007) and children aged 7 to 15 years (p=0.01). Similarly, adults aged 16 to 25 years were at significantly higher risk of graft rejection than children aged under 7 years (p=0.006) and children aged 7 to 15 years (p=0.04).

	Evidence from 1 case series suggests that rates of overall survival and event free survival at 2 years are worse in adults with TDT who have allogenic HSCT compared with children, but there is no difference in rates of acute and chronic GVHD based on age. By contrast, a second case series provides conflicting information on transplant-related complications and suggests acute GVHD and graft failure occur more often in adults compared with children. This evidence is inconclusive.
Subgroup: type of donor	In a case control study (Caocci et al. 2017, n=97 adults who had HSCT), 23-year overall survival and event free survival were significantly higher in adults who had matched sibling HSCT compared with matched unrelated HSCT (78.0% vs 57.6%, p=0.014 and 76.5% vs 53.5%, p=0.006, respectively). Unrelated HSCT was associated with a higher rate of acute GVHD and chronic GVHD (OR 12.5, 95% CI 2.42 to 64.77, p=0.003 and OR 6.77, 95% CI 1.07 to 42.95, p=0.042, respectively). **Evidence from a case control study suggests that rates of overall survival, event free survival, and acute and chronic GVHD are better in adults with TDT who have matched sibling HSCT compared with those who have matched unrelated HSCT. However, this evidence is based on analyses of small subgroups and is inconclusive.**
Subgroup: conditioning regimen	In a case control study (Caocci et al. 2017, n=97 adults who had HSCT), no significant difference was found in 23-year overall survival or event free survival in adults with a busulfan-based conditioning regimen compared with a treosulfan-based regimen. **Evidence from a case control study suggests that rates of overall survival and event free survival are similar whether adults with TDT and allogenic HSCT have a conditioning regimen based on busulfan or treosulfan. However, this evidence is based on analyses of small subgroups and is inconclusive.**

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients can have moderate – severe problems with walking
- **ability to provide self-care:** Patients can have moderate - severe problems with washing or dressing
- **undertaking usual activities:** Patients can have moderate – severe problems with activities of daily living
- **experience of pain/discomfort:** Patients can have moderate – severe pain or discomfort
- **experience of anxiety/depression:** Patients can experience moderate to severe episodes of anxiety or depression during their lifetime

Further details of impact upon patients:
Transfusion Dependent Thalassaemia (TDT) has a profound impact on daily life of patients living with the condition. Patients can suffer from extreme fatigue, exhaustion, breathlessness, palpitations, bone pain (mostly due to the bone marrow going into overdrive), headaches, lack of concentration, cognition disturbances, low mood, anxiety, depression and insomnia.

Pain and fatigue can often increase before and after transfusion. Additionally, having to attend hospital for regular blood transfusions can have a major impact on patients quality of life.

Further details of impact upon carers:
TDT can lead to a high burden on the carer to help with the daily management of chronic illnesses and self-care tasks (bathing, dressing, cooking, and preparing meals, ironing, cleaning the house, getting out and about or help using mobility aids) which may be difficult or impossible for the patient depending on prognosis.

Considerations from review by Rare Disease Advisory Group
Not Applicable.

Pharmaceutical considerations
Inclusion criteria Patients who are aged 18 years and over and who meet the below criteria should be considered for allo-HSCT: • Diagnosis of transfusion dependent thalassaemia AND • Comprehensive organ assessment including but not limited to cardiac, liver, renal assessment[1] AND • Agreement at National Haemoglobinopathy Panel (NHP) AND • At least one first degree relative willing to act as a donor and confirmed as a fully matched sibling donor. **Exclusion criteria** • Current cardiac iron overload T2* < 20 milliseconds • Glomerular Filtration Rate < 40 ml/min/1.73m^2 • Current pregnancy or breastfeeding The prescribing clinician should be aware of the special warnings and precautions for use of the treatment as detailed in the Summary of Product Characteristics.

Considerations from review by National Programme of Care

The proposal received the full support of the Blood and Infection Programme of Care on 6 September 2022.