

**Urgent Clinical Commissioning
Policy Statement:
Allogeneic stem cell
transplantation for adults with
Primary Immune Deficiency
disorders**

NHS England Reference: 170037P



1 Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of this policy statement, we have:

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

In the interests of delivering an urgent commissioning position, a rapid initial equality impact assessment has been carried out.

2 Background

Primary immune deficiency (PID) disorders are a rare group of genetic diseases that are classified according to the nature of the deficiency (severe combined immunodeficiency, combined immune deficiency with or without associated disorders, antibody deficiency, phagocytic disorders, immune regulatory disorders and innate immune defects). There are over 300 different genetic forms of PID described, with an estimated prevalence of 4200 patients in the UK. Although the treatments vary according to the precise disorder and its complications, common treatments include immunoglobulin infusions, the use of anti-microbial drugs and biological (monoclonal antibody) therapies. Other treatments are directed at specific complications that may occur in this group of patients, for example chemotherapy in patients who develop cancer, or supportive therapies (e.g. oxygen therapy, haemodialysis) in patients who have incurred damage to vital organs (such as the lungs or kidneys). None of the above treatments are curative.

A subgroup of patients with PID develop very severe complications including life-threatening infections, bone marrow failure, autoimmune and auto-inflammatory diseases, cancers, and secondary haemophagocytic syndrome (a potentially fatal condition caused by uncontrolled proliferation of white blood cells). For these patients a treatment known as allogeneic stem cell transplantation is likely to be life-saving.

Allogeneic stem cell transplantation replaces the patient's blood and immune systems with those from a healthy donor. The process results in establishment of normal immune system functions in the patient.

The procedure involves two steps:

- (1) conditioning with chemotherapy and/or radiotherapy to remove the patient's blood-forming cells in the bone marrow and to suppress the immune system;
- (2) the infusion of blood stem cells from a healthy donor who is fully or partially matched to the patient.

Most patients with severe combined immune deficiency (or 'SCID') present shortly after birth and require immediate intervention, but other forms of immune deficiency may present in later childhood or adulthood. The total number of allogeneic stem cell transplants performed for PID patients in the UK is at present approximately 60-70/year.

Allogeneic stem cell transplantation is an intensive procedure with the potential for serious complications. Patients therefore undergo careful selection by dedicated, multi-disciplinary transplant teams located in highly specialized transplant centres and only a minority of patients will be suitable for treatment. The decision to proceed to allogeneic stem cell transplantation is based on clinical features, immune cell numbers and function, infectious and non-infectious complications and anticipated clinical course without transplantation. The risks of transplant are increased considerably in patients who have already sustained damage to their vital organs (for example to kidneys or lungs) and in patients with uncontrolled infection or inflammation.

Allogeneic stem cell transplantation is routinely commissioned by NHS England for patients with PID who are aged 18 years or less. Allogeneic stem cell transplantation is not commissioned for adult patients with PID aged >18 years. The current policy therefore does not allow access to treatment for patients with PID who present in adulthood, or patients who presented in childhood and did not require allogeneic stem cell transplantation but may now benefit from the treatment, due to disease progression.

Recent research suggests that outcomes for adult patients with PID undergoing an allogeneic stem cell transplant are good, and similar to those for younger patients. For this reason, NHSE is in the process of developing an 'All Ages' clinical commissioning policy for allogeneic stem cell transplantation for PID with an expected completion date at the end of 2018. However, there are a very small number of adult PID patients who are at risk of imminent, life-threatening or irreversible harm if they cannot receive an allogeneic stem cell transplantation before the clinical commissioning policy process has been completed. These patients are at high risk of early death or the development irreversible complications associated with a high morbidity, cost and impaired quality-of-life. These patients are likely no longer to be fit for transplantation when the 'All Ages' policy is eventually published, due to disease progression.

Adult PID patients who are at risk of imminent, life-threatening or irreversible harm without allogeneic stem cell transplantation are classified into four categories:

1. PID patients with bone marrow failure requiring long-term blood, platelet or cytokine support due to the high risk of (i) uncontrolled infection or bleeding, (ii) transfusion-associated iron overload affecting liver or cardiac function or (iii) alloimmunisation, a complication of transfusion that increases the risk of stem cell transplant rejection.
2. PID patients with lymphoma or other cancers where delays in allogeneic stem cell transplantation will increase the risk of treatment resistance or relapse/cancer progression.
3. Patients meeting the diagnostic criteria for secondary haemophagocytic lymphohistocytosis (HLH) as a result of their PID disorder. HLH is a life-threatening multi-system inflammatory disorder that requires intensive treatment. Urgent allogeneic stem cell transplantation is indicated in patients where (i) there is a documented genetic cause for PID and a high risk of HLH recurrence or (ii) the genetic cause for the PID is not known, but where HLH is refractory to treatment or has relapsed following treatment.
4. Patients who have developed vital organ complications (e.g. to the kidney, lung, gut) as a result of their PID which have failed to respond to alternative treatments and where delay will lead to irreversible organ injury, thus precluding future transplant or significantly increasing the risk of complications.

3 Evidence Summary

NHS England has considered the evidence submitted as part of the preliminary policy proposal to establish the urgent clinical commissioning policy statement, including the clinical criteria for initiating and discontinuing the intervention. This includes the most clinically impactful publications, identified using a literature search strategy defined by the clinical lead. These publications are summarised below:

Publication 1

Fox et al. Successful outcome following allogeneic stem cell transplantation for adult patients with primary immunodeficiencies. Blood 2017 (in press)

The aim of the study was to determine outcomes following allogeneic stem cell transplantation of adult patients with PID. The study was a case series of 29 consecutive adult patients with a variety of PID disorders (mean age 24 years, range 17-50 years) treated at two UK transplant centres using reduced intensity allogeneic stem cell transplantation from 2004-2016. Although the majority of the patients had multiple co-morbidities, overall survival at 3 years was 85.2%. At last follow up, 87% of patients had no evidence of persistent or recurrent infections and none had chronic graft-versus-host disease requiring immune suppression. Good functional immune reconstitution allowed cessation of

immunoglobulin replacement therapy in 89% of patients. These transplant outcomes are very similar to those reported for PID in paediatric populations. Potential limitations of the study are its retrospective design; thus, the outcomes observed could have resulted from selection. However, PID disorders are extremely rare, and randomised controlled studies in paediatric or adult patients are not possible. Case control studies are also not feasible because of the heterogeneity of the PID population and the requirement for large sample sizes.

Publication 2

Gungor et al. Reduced intensity conditioning and HLA-matched haematopoietic stem cell transplantation in patients with chronic granulomatous disease; a prospective, multicentre study. Lancet 2014, 383; 436-48.

The aim of this phase II, multi-centre, prospective and single arm study was to evaluate the safety and efficacy in 56 paediatric and adult patients with one of the most common forms of PID, chronic granulomatous disease. The 2-year probability of survival was 96%. Of note, nearly 1 in 4 patients were aged >18 years and their outcomes were no different to the younger patients. This study has the advantage that it is a prospective study and performed at multiple centres.

4 Commissioning Position

Rationale for a clinical commissioning policy statement

There are overriding patient safety or other clinical issues that require an immediate clinical commissioning position to be implemented.

Recent research suggests that outcomes for adult patients with PID undergoing an allogeneic stem cell transplant are favourable and similar to younger patients. For this reason, NHSE is in the process of developing an 'All Ages' clinical commissioning policy for allogeneic stem cell transplantation for PID with an expected completion date at the end of 2018. However, there are a very small number of adult PID patients who are at risk of imminent, life-threatening or irreversible harm if they cannot receive an allogeneic stem cell transplantation before the clinical commissioning policy process has been completed. Such patients are at high risk of early death or the development of debilitating complications associated with a high morbidity, cost and impaired quality-of-life. These patients are likely no longer to be fit for transplantation when the 'All Ages' policy is eventually published, due to disease progression.

Clinical commissioning position

Based on a limited scoping of the evidence, NHS England has concluded that there is sufficient evidence to support for the routine commissioning of this treatment for the indications and clinical criteria listed.

Clinical commissioning criteria

A. Eligibility will be based upon the following:

1. Adult patient with PID meeting one or more of the following 4 categories:
 - PID patients with bone marrow failure requiring long-term blood, platelet or cytokine support due to the high risk of (i) uncontrolled infection or bleeding, (ii) transfusion-associated iron overload affecting liver or cardiac function or (iii) alloimmunisation, a complication of transfusion that increases the risk of stem cell transplant rejection.
 - PID patients with lymphoma or other cancers where delays in allogeneic stem cell transplantation will increase the risk of treatment resistance or relapse/cancer progression.
 - Patients meeting the diagnostic criteria for secondary haemophagocytic lymphohistocytosis (HLH) as a result of their PID disorder. HLH is a life-threatening multi-system inflammatory disorder that requires intensive treatment. Urgent allogeneic stem cell transplantation is indicated in patients where (i) there is a documented genetic cause for PID and a high risk of HLH recurrence or (ii) the genetic cause for the PID is not known, but where HLH is refractory to treatment or has relapsed following treatment.
 - Patients who have developed vital organ complications (e.g. to the kidney, lung, gut) as a result of their PID which have failed to respond to alternative treatments and where delay will lead to irreversible organ injury, thus precluding future transplant or significantly increasing the risk of complications.
2. An allogeneic stem cell transplant is agreed by an expert multi-disciplinary team to be necessary urgently in order to avoid irreversible disease progression, end organ damage, or death. The MDT will be drawn from major PID centres across England. As a minimum the MDT will include:
 - 2 consultant immunologists from independent centres with expertise in managing PID
 - 2 consultant haematologists from independent centres with expertise in stem cell transplantation
 - A consultant haematologist with expertise in treating teenage and young adults
 - A consultant with expertise in infectious disease
 - A hospital pharmacist
 - A clinical psychologist

- A clinical nurse specialist with expertise in immunology or haematology
- Invited experts according to the specific issues relevant to the patient being discussed (e.g. radiology, cardiac, renal consultants).

A nominated consultant will chair the MDT and co-ordinate discussions through NHS secure email and/or teleconference. MDT outcomes will be recorded using a standard pro forma and included in the patient notes.

B. Treatment

It is expected that the majority of transplants carried out under this urgent policy statement will be performed at Newcastle Hospitals NHS Foundation Trust and at University College Hospital London NHS Foundation Trust, both of which have developed integrated, adult PID transplant services and receive the majority of referrals for this procedure. In selected cases it may occasionally be considered more appropriate clinically for the procedure to be undertaken by an alternative centre, where this is advised by the national MDT. NHS England must be informed of any adult PID transplant which will be undertaken in a centre other than the two designated providers.

The criteria for selection of centres commissioned to undertake allogeneic transplants for PID will be considered formally as part of the development of the full 'all ages' clinical commissioning policy.

Clinical commissioning policy development plan

A full 'all ages' commissioning policy is already being developed. Should the subsequent published commissioning policy be revised to 'not routinely commissioned', patients started on treatment under this policy statement will continue to have access to it provided they and the clinician responsible for their care continue to believe that it is the right treatment for them.

5 Mechanism for funding

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

6 Date of policy statement approval and review

The policy statement is effective from January 2018.

The full clinical commissioning policy is in development. Interested stakeholders can express interest in the development of the policy by contacting ENGLAND.npoc-bloodandinfection@nhs.net.

This policy statement will be formally reviewed by April 2019.

7 References

Fox et al. Successful outcome following allogeneic stem cell transplantation for adult patients with primary immunodeficiencies. *Blood* 2017 (*in press*)

Gungor et al. Reduced intensity conditioning and HLA-matched haematopoietic stem cell transplantation in patients with chronic granulomatous disease; a prospective, multicentre study. *Lancet* 2014, 383; 436-48.