NHS England

Evidence review: Allogeneic haematopoietic stem cell transplant for primary immunodeficiencies (adults)

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Contents

1 Introduction

Introduction

- Primary immunodeficiencies (PID) are a group of rare inherited diseases characterised by severe dysfunction of adaptive and/or innate immunity (Fox et al 2018). They include the following sub-groups of conditions: severe combined immune deficiency (SCID); combined immune deficiency (CID); CID with associated features; antibody deficiencies; immune dysregulation, including haemophagocytic disorders, lymphoproliferative disorders, autoimmune disease and early onset inflammatory bowel disease; phagocytic cell disorders; innate defects (NHS England 2018).
- Nearly 300 distinct immunodeficiencies have been described, with 20 specific diseases accounting for 90% of cases (Fox et al 2018). There are also categories of 'unspecified' and 'other' (NHS England 2018).
- There are many variations in clinical manifestations (NHS England 2018). Patients with severe PID may present with serious or life-threatening infections, auto-inflammatory disease, inflammation, organ damage as a result of treatment and repeated infections and complications from a dysfunctional immune system such as malignancy (NHS England 2018).
- Untreated PID can lead to ongoing recurrent, progressive or life threatening infection, autoimmunity and malignant disease and result in poor quality of life and early death (NHS England 2018).

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

- No NICE guidance on allogeneic haematopoietic stem cell transplant (HSCT) for PID was identified.

The indication and epidemiology

- The exact prevalence of PID in the UK is not known, but a high level estimate for the number of people with PID in England is approximately 4,200 (NHS England, 2018).
- Only a small proportion of PID patients will be suitable and will meet the criteria for HSCT (NHS England 2018).
- Between 2013 and 2016, 60 to 68 people per year received HSCT for PID. This included between 2 and 4 adults per year, funded via individual funding requests (NHS England 2018).
- It is anticipated that in the UK, up to 10 adult patients with PID per year will meet the criteria for HSCT and have an appropriate donor (NHS England 2018).

Standard treatment and pathway of care

- Early HSCT is important for infants and children presenting with serious or life-threatening infections (Fox et al 2018). Children with severe PID rarely survive past the first year of life without definitive treatment (Fox et al 2018).
- However, the clinical phenotype of PIDs is heterogeneous and a variety of factors may result in patients surviving to adolescence or adulthood without HSCT, for example, a milder clinical phenotype, delayed diagnosis, late presentation, lack of a genetic diagnosis, or lack of a suitable donor (Fox et al 2018).
- For adults, treatment includes immunoglobulin (IVIg) replacement therapy for patients with B cell deficits, systemic immunosuppressive therapy for patients with auto-inflammatory/ immune dysregulation complications, chemotherapy for patients with PID-associated malignancies and broad spectrum antimicrobials (including anti-virals and anti-fungals) for

patients with susceptibility to infections (NHS England 2018).

- Allogeneic HSCT is a potentially curative treatment (NHS England 2018). The only other potentially curative treatment is gene therapy; however, this is only available for selected monogenic immunodeficiencies within clinical trials and is currently an experimental treatment (NHS England 2018).

The intervention (and licensed indication)

- In allogeneic HSCT (also known as bone marrow transplantation), the patient's own bone marrow stem cells are replaced with healthy stem cells from a tissue-type matched or mismatched[1] donor (NHS England 2018).
- Patients may receive a conditioning regimen prior to HSCT to help prevent rejection of the transplanted cells. This can include chemotherapy, monoclonal antibody therapy or radiation (NCI 2017).
- Not all patients with PID require HSCT. The decision to proceed with HSCT is made by an expert multi-disciplinary team, based on immune cell numbers and function, infectious and non-infectious complications including risk of malignancy, anticipated clinical course without HSCT and failure to respond to alternative therapies (NHS England 2018).

Rationale for use

- The inherited genetic mutation in PID affects immune cells derived from bone marrow stem cells. Therefore replacing the mutation-carrying cells with healthy stem cells has the potential to cure the immune deficiency (NHS England 2018), resulting in the production of healthy immune cells.
- Allogeneic transplantation has a relatively high mortality and morbidity which must be weighed against the potential longer-term survival benefits and opportunity for cure of an inherited disease (NHS England 2018).

2 Summary of results

- Twelve uncontrolled studies were included in this evidence review (Albert et al 2018; Fox et al 2018; Jin et al 2018; Leiding et al 2018; Parta et al 2017; Shah et al 2017; Fu et al 2016; Oshima et al 2015; Wehr et al 2015; Grossman et al 2014; Güngör et al 2014; Spinner et al 2014). Four studies reported outcomes for adults or adults/adolescents (Fox et al 2018; Jin et al 2018; Fu et al 2016; Grossman et al 2014) and the remaining eight studies had mixed populations of adults and children from which data on outcomes for adult patients were extracted. Study sample sizes ranged from four to 29 and median follow-up (when reported) ranged from 14 months to five years. No studies compared HSCT with alternative treatment strategies.

Clinical effectiveness

- Overall survival (11 studies, total n=158; range 4 to 29). Overall survival ranged from 54% to 100%, and was at least 80% in eight of the 11 studies. For the seven studies reporting median follow-up for overall survival this ranged from 14 months to five years. One study

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

described overall survival for eight patients who received HSCT (88%) and 10 patients who did not receive HSCT[2] (20%) (p=0.006). No studies reported 95% confidence intervals (CI).

- Event-free survival (4 studies, total n=68; range 4 to 29). Event-free survival ranged from 71% to 100%, and was at least 90% in three of the four studies (95%CI not reported). For the three studies reporting median follow-up this ranged from two to five years.
- Post-transplant infection (8 studies, total n=92; range 4 to 29). The proportion of patients experiencing any post-transplant infection ranged from 20% to 100% with median follow-up (where reported) from 20.9 months to 3.5 years. More commonly reported infections included cytomegalovirus (CMV) reactivation, respiratory infections, sepsis, fungal infections and Epstein Barr virus (EBV) reactivation. No grading system was reported to indicate the seriousness of the infections.
- Engraftment[3] (11 studies, total n=141; range 4 to 29). The reporting of this outcome varied. Nine studies reported graft failures/ rejections[4]. In five studies there were no graft failures or rejections. In four studies the proportion of graft failures ranged from 8% to 50%. More of these were secondary graft failures (six cases) than primary graft failures (three cases)[5]. Median time to neutrophil engraftment[6] was between 12 and 15 days in four studies. In three studies, median time to platelet engraftment (defined as >20 x 10^9/L for seven consecutive days) was between 13 and 21 days and was 14 days in a fourth study (defined as ≥50 x 10^9/L). A further study reported median time to white blood cell viability as 11.5 days and median time to platelet engraftment as 13 days (without further definition of these outcomes).
- Chimerism[7] (8 studies, total n=106; range 4 to 29). The reporting of this outcome varied with different cut-off values and timescales for assessing 'complete' or 'full' chimerism. For example, in one study 94% of patients achieved complete chimerism (donor DNA >90%[8]) and in another study 48% achieved multi-lineage[9] full donor chimerism (donor DNA ≥97%[10]). Most studies reported chimerism rates of 100% or around 97% to 99% for almost all patients.
- Immune reconstitution (3 studies, total n=60; range 13 to 29). The reporting of this outcome varied. In the three individual studies respectively: 94% of patients had ceased immunosuppression and intravenous immunoglobulin; 89% of 9 patients who were receiving replacement pre-transplantation had ceased monthly immunoglobulin and 76% were not receiving immunosuppression at last follow-up; and 100% were off immunosuppressants.

Safety

- Transplant-related mortality (2 studies, total n=47; range 18 to 29). Two studies reported a transplant-related mortality of 6% (one patient) and 14% (four patients) respectively. Causes of death were multi-organ failure secondary to sepsis (two patients),

[2] No reasons were reported for why these patients did or did not receive HSCT
[3] 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 cells
[4] Defined by Albert et al (2018) as <10% donor cells with disease recurrence
[5] Patients with primary graft failure did not engraft after first transplantation. Patients with secondary graft failure had failure after initial engraftment (Parta et al 2017)
[6] Most commonly defined as >0.5 x 10^9/L for 3 consecutive days
[7] the presence of donor cells
[8] As defined in Albert et al (2018)
[9] Chimerism is often reported by cell lineage i.e. for peripheral blood mononuclear cells, T-cells, B-cells and granulocyte compartments
[10] As defined in Fox et al (2018)

granulomatous meningoencephalitis (one patient), sepsis in the context of extensive chronic graft-versus-host disease (one patient) and adenovirus (one patient). In a third study (n=4) mortality was 100%, however the study authors did not specify that these deaths were transplant-related.

- Graft-versus-host disease[11] (GvHD) (10 studies, total n=124; range 4 to 29). In nine studies the proportion of patients experiencing any acute GvHD ranged from 25% to 80%. Most patients experienced mild to moderate acute GvHD. In four studies with any cases of severe to life threatening acute GvHD, the proportion of patients affected was between 3% and 21%. In one study there were no cases of moderate to life threatening GvHD but the proportion of patients experiencing mild acute GvHD, if any, was not reported. Seven studies reported the proportion of patients experiencing any chronic GvHD as ranging from 0% to 60%. In the two studies that specified the severity of the chronic GvHD this was mild in most patients. One study did not report acute and chronic GvHD separately, but reported that 21% of patients experienced severe or life threatening acute GvHD or extensive[12] chronic GvHD.
- Transplant-related complications (non-infectious) (4 studies, total n=50; range 4 to 29). The proportion of patients experiencing transplant-related complications in three of the studies ranged from 46% to 75%, with a fourth study stating that there were four complications within their study population (n=4) but not specifying how many patients were affected. Only one of these studies reported median follow-up which was 31 months. Examples of complications included requirement for donor lymphocyte infusions, multi-organ failure, EBV post-transplant lymphoproliferative disease, renal impairment, prolonged cytopenias, severe transfusion-dependent thrombocytopenia, gastrointestinal haemorrhage and transient red-cell aphasia. No grading system was reported to indicate the seriousness of the complications reported.

Cost-effectiveness

- No studies were identified reporting the cost-effectiveness of allogeneic HSCT in adults with PID compared with alternative treatment strategies.

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). Due to the breadth of the population for this review the search looked for studies on 'primary immune deficiencies' (PID) generally and also for selected PIDs specified by the NHS England Policy Working Group.
- 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.

[11] In 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 after transplant. Acute GvHD is graded as I = mild; II = moderate; III = severe; IV = life threatening (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf). Chronic GvHD is graded as mild; moderate; severe (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)

[12] Not further defined

- The titles and abstracts of the results from the literature search 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.
- The studies matching the PICO after review of the full text were discussed with NHS England before the final study selection (September 2018). This led to the identification of two studies that were not returned by the search, as the PID (GATA2 deficiency) was not one of the PID conditions specifically searched for and the study authors did not use any of the generic search terms. These studies were reviewed at full text and included in the review.
- No comparative studies were identified. Therefore uncontrolled studies including data for more than one patient who was an adult at the time of HSCT were included, if separate data on adults could be extracted or the focus of the study was adults or adults/adolescents. Studies with mixed populations of children and adults with no separate reporting of outcomes for adults were not eligible for inclusion.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using the National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8).

4 Results

This evidence review identified 12 studies of patients who received HSCT for PID. Four of these reported outcomes for adults or adults/adolescents who received HSCT for PID (Fox et al 2018; Jin et al 2018; Fu et al 2016; Grossman et al 2014) and eight reported outcomes for mixed populations of children and adults from which data on outcomes for adult patients were extracted (Albert et al 2018; Leiding et al 2018; Parta et al 2017; Shah et al 2017; Oshima et al 2015; Wehr et al 2015; Güngör et al 2014; Spinner et al 2014). All 12 studies were uncontrolled with sample sizes ranging from four to 29. The median follow-up (when reported) ranged from 14 months to five years. Full details of the study designs and outcomes are summarised in the evidence tables in section 7.

1. What is the evidence for the clinical effectiveness of allogeneic HSCT in adults with primary immunodeficiencies, compared with any alternative treatment strategies?

No studies compared HSCT with alternative treatment strategies.

Clinical outcomes reported in the 12 uncontrolled studies included overall survival, event-free survival, post-transplant infection, engraftment, chimerism and immune reconstitution.

Overall survival

Overall survival was reported by 11 studies which included a total of 158 patients (range 4 to 29) (Albert et al 2018; Fox et al 2018; Jin et al 2018; Parta et al 2017; Shah et al 2017; Fu et al 2016; Oshima et al 2015; Wehr et al 2015; Grossman et al 2014; Güngör et al 2014; Spinner et al 2014). This ranged from 54% to 100% with a median follow-up (where reported) of between 14 months and five years. In eight of the 11 studies overall survival was at least 80%. Three of the studies reported overall survival at a fixed time point. In one study (Fox et al 2018, n=29) overall survival was 89% at one year and 85% at three years; in one study (Fu et al 2016, n=4) two year

overall survival was 100%; and in one study (Spinner et al 2014, n=21) overall survival was 72% at one year, 65% at two years and 54% at four years. One study (Jin et al 2018, n=18) described overall survival for eight patients who received HSCT (88%) and 10 patients who did not receive HSCT[13] (20%) (p=0.006). No studies reported 95% confidence intervals.

Event-free survival

Event-free survival was reported by four studies which included a total of 68 patients (range 4 to 29) (Albert et al 2018; Fox et al 2018; Parta et al 2017; Fu et al 2016). This ranged from 71% to 100% with a median follow-up (where reported) of between two and five years. In three of the four studies event-free survival was at least 90%. Two of the studies reported event-free survival at a fixed time point. In one study (Fox et al 2018, n=29) event-free survival was 90% at one and three years; and in one study (Fu et al 2016, n=4) two year event-free survival was 100%. No studies reported 95% confidence intervals.

Post-transplant infection

Post-transplant infection was reported by eight studies which included a total of 92 patients (range 4 to 29) (Fox et al 2018; Jin et al 2018; Leiding et al 2018; Shah et al 2017; Fu et al 2016; Oshima et al 2015; Grossman et al 2014; Güngör et al 2014). The proportion of patients experiencing any post-transplant infection ranged from 20% to 100% with a median follow-up (where reported) ranging from 20.9 months to 3.5 years. More commonly reported infections included CMV reactivation, respiratory infections, sepsis, fungal infections and EBV reactivation. No grading system was reported to indicate the seriousness of the infections reported.

Engraftment[14]

Engraftment was reported by 11 studies which included a total of 141 patients (range 4 to 29) (Albert et al 2018; Fox et al 2018; Jin et al 2018; Leiding et al 2018; Parta et al 2017; Shah et al 2017; Fu et al 2016; Oshima et al 2015; Wehr et al 2015; Grossman et al 2014; Güngör et al 2014). The reporting of this outcome varied. Nine studies reported graft failures/ rejections[15]. Five studies (Albert et al 2018; Fox et al 2018; Shah et al 2017; Fu et al 2016; Oshima et al 2015) specified that there were no graft failures/ rejections. Four studies (Leiding et al 2018; Parta et al 2017; Wehr et al 2015; Güngör et al 2014) specified a proportion of graft failures which ranged from 8% to 50%. More of these were secondary graft failures (six cases) than primary graft failures (three cases)[16]. Some studies reported the median days to neutrophil and platelet engraftment using varying definitions. Median time to neutrophil engraftment[17] was between 12 and 15 days in four studies (Fox et al 2018; Shah et al 2017; Fu et al 2016; Grossman et al 2014). Median time to platelet engraftment (defined as >20 x 10^9/L for seven consecutive days) was between 13 and 21 days in three studies (Shah et al 2017; Fu et al 2016; Grossman et al 2014) and in a fourth study (Fox et al 2018) was 14 days when defined as ≥50 x 10^9/L. A further study (Jin et al 2018) reported median time to white blood cell viability as 11.5 days and median time to platelet engraftment as 13 days (without further definition of these outcomes).

Chimerism[18]

Chimerism was reported by eight studies which included a total of 106 patients (range 4 to 29) (Albert et al 2018; Fox et al 2018; Jin et al 2018; Shah et al 2017; Fu et al 2016; Oshima et al

[13] No reasons were reported for why these patients did or did not receive HSCT

[14] 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 cells

[15] Defined by Albert et al (2018) as <10% donor cells with disease recurrence

[16] Patients with primary graft failure did not engraft after first transplantation. Patients with secondary graft failure had failure after initial engraftment (Parta et al 2017)

[17] Most commonly defined as >0.5 x 10^9/L for 3 consecutive days

[18] The presence of donor cells

2015; Grossman et al 2014; Güngör et al 2014). The reporting of this outcome varied with different cut-off values and timescales for assessing 'complete' or 'full' chimerism. For example, in Albert et al (2018, n=18), 94% of patients achieved complete (donor DNA >90%) chimerism and in Fox et al (2018, n=29), 48% achieved multi-lineage[19] full donor chimerism (donor DNA ≥97%). Most studies reported chimerism rates of 100% or around 97% to 99% for almost all patients.

Immune reconstitution
Immune reconstitution was reported by three studies which included a total of 60 patients (range 13 to 29) and a median follow-up (where reported) of between 2.6 and five years. The reporting of this outcome varied. In one study (Albert et al 2018, n=18) 94% had ceased immunosuppression and intravenous immunoglobulin; in one study (Fox et al 2018, n=29) 89% of 9 patients who were receiving replacement pre-transplantation had ceased monthly immunoglobulin and 76% were not receiving immunosuppression at last follow-up; and in one study 100% were off immunosuppressants (Güngör et al 2014, n=13).

2. What is the evidence on safety of allogeneic HSCT in adults with primary immunodeficiencies, compared with any alternative treatment strategies?

No studies compared HSCT with alternative treatment strategies.

Safety outcomes reported in the 12 uncontrolled studies included transplant-related mortality, graft-versus-host disease and (non-infectious) transplant-related complications.

Transplant-related mortality
Transplant-related mortality was reported by two studies which included a total of 47 patients (range 18 to 29). Transplant-related mortality was 6% and 14% with median follow-up of five and 2.6 years respectively (Albert et al 2018, n=18; Fox et al 2018, n=29). Causes of death were multi-organ failure secondary to sepsis (two patients), granulomatous meningoencephalitis (one patient), sepsis in the context of extensive chronic graft-versus-host disease (one patient) and adenovirus (one patient). A third study (Leiding et al 2018, n=4, follow-up period not reported) had 100% mortality but did not specify if this was transplant-related.

Graft-versus-host disease[20]
Graft-versus-host disease (GvHD) was reported by ten studies which included a total of 124 patients (range 4 to 29) (Albert et al 2018; Fox et al 2018; Jin et al 2018; Leiding et al 2018; Shah et al 2017; Fu et al 2016; Oshima et al 2015; Wehr et al 2015; Grossman et al 2014; Güngör et al 2014). In nine studies reporting the proportion of patients experiencing acute GvHD by severity grade, 25% to 80% of patients experienced any grade of acute GvHD. In four of these studies all cases of acute GvHD were mild to moderate and in a further four studies, between 13% and 42% of patients experienced mild to moderate GvHD and between 3% and 21% of patients experienced severe to life threatening acute GvHD. In one study (Fu et al 2016) there were no cases of moderate to life threatening GvHD but the proportion of patients, experiencing mild acute GvHD, if any, was not reported. Seven studies reported the proportion of patients experiencing

[19] Chimerism is often reported by lineage i.e. for peripheral blood mononuclear cells, T-cells, B-cells and granulocyte compartments

[20] In 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 after transplant. Acute GvHD is graded as I = mild; II = moderate; III = severe; IV = life threatening (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf). Chronic GvHD is graded as mild; moderate; severe (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)

any chronic GvHD as ranging from 0% to 60%. In the two studies that specified the severity of the chronic GvHD this was mild in all patients (Albert et al 2018) and mild or severe in 14% and 7% of patients respectively (Grossman et al 2014). One study (Wehr et al 2015) did not report acute and chronic GvHD separately, but reported that 21% of patients experienced severe or life threatening acute GvHD or extensive[21] chronic GvHD.

Transplant-related complications
Transplant-related complications (non-infectious) were reported by four studies which included a total of 50 patients (range 4 to 29) (Fox et al 2018; Leiding et al 2018; Fu et al 2016; Güngör et al 2014). The proportion of patients experiencing any transplant-related complications in three of the studies ranged from 46% to 75%, with a fourth study (Fu et al 2016) stating that there were four complications within their study population (n=4) but not specifying the number of patients affected. Only one of these studies (Fox et al 2018) reported median follow-up which was 31 months. Examples of complications included requirement for donor lymphocyte infusions, multi-organ failure, EBV post-transplant lymphoproliferative disease, renal impairment, prolonged cytopenias, severe transfusion-dependent thrombocytopenia, gastrointestinal haemorrhage and transient red-cell aphasia. No grading system was reported to indicate the seriousness of the complications reported.

3. What is the evidence for the cost-effectiveness of allogeneic HSCT in adults with primary immunodeficiencies, compared with any alternative treatment strategies?

No studies were identified reporting the cost-effectiveness of allogeneic HSCT in adults with PID compared with alternative treatment strategies.

5 Discussion

Twelve uncontrolled studies reported clinical and safety outcomes for a total of 162 patients who received HSCT for PID. This included four studies reporting outcomes for adults/adolescents and eight studies reporting outcomes for mixed populations of children and adults from which data on outcomes for adult patients could be extracted. The studies were small with the sample sizes of the individual studies ranging from four to 29 patients and median follow-up (when reported) ranged from 14 months to five years.

Descriptive results from small, uncontrolled studies reported generally positive outcomes for adults with PID receiving HSCT with most studies reporting overall survival of at least 80%. Some studies reported that high proportions of patients experienced complications, reflecting the seriousness of PID and the risks associated with HSCT; however, the degree of severity was not always clear. The studies do not provide evidence for the effectiveness of HSCT compared to alternative treatment strategies.

Eight of the 12 studies had a retrospective design which introduces the possibility of selection bias in the study population. The authors of three studies stated that they were prospective, but in two of these no information was provided about how the data on outcomes was collected, making the risk of bias unclear. One study did not report the study design, also resulting in an unclear risk of bias.

[21] Not further defined

Three of the 12 studies did not report details of the number of treatment centres that patients were drawn from or the years in which patients were treated. Three studies included patients treated at centres worldwide over a long period of time (nine to 19 years). The remaining six studies included patients treated at either one or two centres in the same country over time periods of between seven and 21 years. The inclusion of patients over a long time period or from multiple centres reflects the rarity of the condition and intervention. However, it also introduces potential sources of bias around differences in practices between centres or over time.

6 Conclusion

The best evidence considering the effectiveness of HSCT for adults with PID comes from descriptive outcomes from small uncontrolled studies.

The uncontrolled studies generally describe positive survival and other clinical outcomes for patients with some reporting high rates of complications reflecting the seriousness of PID and the risks associated with HSCT. The studies do not provide evidence for the effectiveness of HSCT compared to alternative treatment strategies.

Overall, the evidence base is limited to uncontrolled, mostly retrospective studies which are at risk of selection bias. The limitations of the evidence base limit the strength of any conclusions that can be drawn.

7 Evidence Summary Table

For abbreviations see list after each table

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Albert et al 2018	S2 Retrospective case series of patients treated at 1 German centre between 2007 and 2014	n=18 Adults/ adolescents with PID Number of pre-transplant risk factors[22] • 0: 7/18 (39%) • 1: 10/18 (56%) • 2:1/18 (6%) Mean Lansky/Karnofsky score[23] at HSCT: 92% (range 80 to 100) Patients had a variety of	Allogeneic HSCT	Primary Clinical Effectiveness	Overall survival	Median follow-up: 5 years (range 2 to 9) 17/18 (94%) were alive at last follow-up	6	Direct	This small, uncontrolled retrospective review included patients from 1 centre in Germany treated over an 8 year period This study also included data for a group of 43 children. Only the results for the group of 18 adult/adolescent patients are extracted here The adult/adolescent patients were aged 15 to 22 years at HSCT. The proportion of patients who were 18 years or older is not known The retrospective design of the study introduces the possibility of selection bias in the study population, e.g. from the completeness or classification of details from patient records As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments
				Primary Clinical Effectiveness	Event-free survival	Median follow-up: 5 years (range 2 to 9) 17/18 (94%) were event-free at last follow-up			
				Primary Clinical Effectiveness	Engraftment	Median follow-up: 5 years (range 2 to 9) No patients had graft failure or rejection			
				Primary Clinical Effectiveness	Chimerism	Median follow-up: 5 years (range 2 to 9) • Complete (>90% donor DNA): 17/18 (94%) • Mixed (10% to 90% donor DNA): 1/18 (6%)			
				Primary	Immune reconstitution	Median follow-up: 5 years (range 2 to 9)			

[22] Including active infection at the beginning of conditioning, presence of an active steroid-dependent inflammatory disease or pre-existing malignancy

[23] Karnofsky/ Lansky scores are used to determine functional status. The Karnofsky Scale is designed for people aged ≥16 years and the Lansky Scale for people <16 years old. Both scales are scored from 10 to 100 with higher scores indicating better function. 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. A score of 80% is defined as “”normal activity with effort” on the Karnofsky Scale and “restricted in strenuous play, tires more easily, otherwise active” on the Lansky scale (https://www.cibmtr.org/DataManagement/TrainingReference/Manuals/DataManagement/Documents/appendix-l.pdf)

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		PIDs, including 6 patients with CGD Median age at HSCT: 18.5 years (range 15 to 22)		Clinical Effectiveness		17/18 patients (94%) ceased immunosuppression and IVIG			
				Primary Safety	Transplant-related mortality	Median follow-up: 5 years (range 2 to 9) 1/18 patients (6%) Cause of death: adenovirus			
				Primary Safety	Graft-versus-host disease Acute GvHD graded using the modified Glucksberg criteria[24] Chronic GvHD graded using the National Institutes of Health consensus standards[25]	Median follow-up: 5 years (range 2 to 9) **Acute GvHD** • Grade I: 9/18 (50%) • Grade II: 2/18 (11%) No patients had grade III or IV acute GvHD **Chronic GvHD** • Mild: 4/18 (22%) No patients had moderate or severe chronic GvHD			
Fox et al 2018	S2 Retrospective case series of patients treated at 2 UK centres	n=29 Adults with PID who had developed complications that necessitated definitive	Allogeneic HSCT	Primary Clinical Effectiveness	Overall survival	Mean follow-up: 3.5 years (range 4 months to 12 years); median follow-up: 31 months (i.e. 2.6 years) (range not specified) • At 1 year: 89% • At 3 years: 85% 95%CI not reported	6	Direct	This small, uncontrolled retrospective review included patients from 2 UK centres treated over a 12 year period The study authors also reported separate results for CGD compared to other PIDs and by donor source. These results are not within scope of this review and are not reported Patients were aged 17 to 50 years at HSCT. The

[24] Graded as I = mild; II = moderate; III = severe; and IV = very severe (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)
[25] Graded as mild; moderate; severe (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	between 2004 and 2016	treatment with curative intent HCT-CI scores[26] pre-transplant 1: 7 (24%) 2: 10 (35%) ≥3: 12 (41%) Patients had a variety of PIDs, including 11 patients with CGD Median age at HSCT: 24 years (range 17 to 50)				24/29 (83%) were alive at last follow-up			outcomes included data for 2/29 patients who were <18 years old at HSCT The median follow-up was relatively short at 2.6 years and no confidence intervals were reported for the survival outcomes so the precision of the results is unclear The retrospective design of the study introduces the possibility of selection bias in the study population, e.g. from the completeness or classification of details from patient records As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments
				Primary Clinical Effectiveness	Event-free survival	Mean follow-up: 3.5 years (range 4 months to 12 years); median follow-up: 31 months (i.e. 2.6 years) (range not specified) • At 1 year: 90% • At 3 years: 90% 95%CI not reported			
				Primary Clinical Effectiveness	Post-transplant infection	Mean follow-up: 3.5 years (range 4 months to 12 years); median follow-up: 31 months (i.e. 2.6 years) (range not specified) 20/29 patients (69%) were described as having infectious complications Infectious included (number of cases) : • CMV reactivation: 5 • EBV reactivation: 3 • Sepsis: 2 • Warts: 2 • HPV: 2 • Respiratory tract infection: 1 • Cystitis: 1 • Recurrent bacterial chest infection: 1			

[26] The HCT-CI is a co-morbidity tool (https://qxmd.com/calculate/calculator_108/hematopoietic-cell-transplantation-specific-comorbidity-index-hct-ci) capturing the prevalence, magnitude and severity of various organ impairments before allogeneic HSCT to predict risk of transplant-related mortality

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• Rhinovirus: 1 • Bilateral lower lobe consolidation: 1 • Multiple infective complications: 1 • Adenoviraemia: 1 • Pulmonary aspergillosis: 1 • Rotavirus diarrhoea: 1			
				Primary Clinical Effectiveness	Engraftment	Mean follow-up: 3.5 years (range 4 months to 12 years); median follow-up: 31 months (i.e. 2.6 years) (range not specified) No patients had graft failure or rejection **Time to neutrophil engraftment** (≥0.5 x 10^9/L[27]): median 12 days (IQR 11 to 17) **Time to platelet engraftment** (≥50 x 10^9/L[27]): median 14 days (IQR 11 to 20)			
				Primary Clinical Effectiveness	Chimerism	Mean follow-up: 3.5 years (range 4 months to 12 years); median follow-up: 31 months (i.e. 2.6 years) (range not specified) For patients with chimerism data at 12 months (n=21), the			

[27] Number of consecutive days required not specified

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						number (%) achieving multi-lineage full donor chimerism (donor DNA ≥97%): 10/21 (48%) Proportion of patients (n=21) with full donor chimerism donor DNA ≥97%) for specific lineages: • Unfractionated PBMC: 85% • T cells: 52% • B cells: 69% • Granulocytes: 67%			
				Primary Clinical Effectiveness	Immune reconstitution	Mean follow-up: 3.5 years (range 4 months to 12 years); median follow-up: 31 months (i.e. 2.6 years) (range not specified) 8/9 (89%) of surviving patients who were receiving replacement pre-transplantation stopped monthly immune replacement post-transplant 22/29 (76%) were not receiving immunosuppression at last follow-up			
				Primary Safety	Transplant-related mortality	Mean follow-up: 3.5 years (range 4 months to 12 years); median follow-up: 31 months (i.e. 2.6 years) (range not specified) 4/29 patients (14%)			

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Cause of death (number of cases): • Multi-organ failure secondary to sepsis: 2 • Granulomatous meningoencephalitis: 1 • Secondary to sepsis in the context of extensive chronic GvHD: 1			
				Primary Safety	Graft-versus-host disease	Mean follow-up: 3.5 years (range 4 months to 12 years); median follow-up: 31 months (i.e. 2.6 years) (range not specified) **Acute GvHD**[28] • Grade I: 8/29 (28%) • Grade II: 4/29 (14%) • Grade III: 1/29 (3%) No patients had grade IV acute GvHD **Chronic GvHD**[29] • Progressed to limited (1 organ) chronic GvHD from acute: 7/29 (24%) • Steroid refractory			

[28] Grading scale not specified but consistent with the modified Glucksberg criteria for acute GvHD (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)
[29] Grading scale not specified

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						extensive chronic GvHD: 1/29 (3%)			
				Primary Safety	Transplant-related complications (non-infectious)	Mean follow-up: 3.5 years (range 4 months to 12 years); median follow-up: 31 months (i.e. 2.6 years) (range not specified) 20/29 patients (69%) were described as having other complications Complications included (number of cases): • Donor lymphocyte infusions: 4 • Multi-organ failure: 2 • EBV PTLD: 2 • Renal impairment: 2 • Prolonged cytopenias: 2 • Idiopathic thrombocytopenic purpura: 1 • Progressive pulmonary fibrosis/ bronchiolitis obliterans: 1 • Papillary renal cell carcinoma: 1 • Oesophageal stricture secondary to peptic ulceration: 1 • CSA-induced neurotoxicity: 1 • Acute thyroiditis: 1			

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• Ovarian failure: 1 • Premature ovarian insufficiency: 1 • Delayed engraftment: 1 • Intermittent neutropenia: 1 • Fibromyalgia: 1 • Chronic fatigue: 1 • Thyrotoxicosis: 1 • Slow recovery of counts and persistent splenomegaly: 1 • Iron and vitamin D deficiency: 1 • Hemophagocytosis: 1 • Granulomatous meningitis: 1 • Acute hepatic failure: 1 • Depression: 1			
Jin et al 2018	S2 Retrospective case series of patients treated at 1 centre in China between 2010 and 2017	n=18 Adults with primary HLH Median age at onset 25.5 years (range 18 to 54) Median age at HSCT not reported	8 patients received allogeneic HSCT[30] 10 patients did not receive HSCT (reason not specified)	Primary Clinical Effectiveness	Overall survival	Patients followed up to May 2017. Median follow-up not reported 7/8 HSCT patients were alive at last follow-up (88%). Median survival 27.2 months 2/10 patients who did not have HSCT were alive at last follow-up (20%). Median survival 7 months	5	Direct	This small, uncontrolled retrospective review included patients from 1 Chinese centre treated over a 7 year period. Median follow-up was not reported This study also reported details of the clinical characteristics of HLH. These details are outside the scope of the review and are not reproduced here Although the survival outcome was retrospectively compared for patients who did or did not receive HSCT, it is not a comparative study. Reasons why these patients did not receive HSCT were not reported The retrospective design of the study introduces the possibility of selection bias in the study population,

[30] The HLH-94 treatment guidance recommends allogeneic HSCT for familial HLH and refractory recurrent HLH patents (Jin et al 2018)

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						The difference between the groups was statistically significant (p=0.006)			e.g. from the completeness or classification of details from patient records As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments
				Primary Clinical Effectiveness	Post-transplant infection	Patients followed up to May 2017. Median follow-up not reported No patients had post-transplant EBV (4 patients had EBV pre-transplant)			
				Primary Clinical Effectiveness	Engraftment	Patients followed up to May 2017. Median follow-up not reported **White blood cell viability**[31]: median 11.5 days (range 8 to 18) **Time to platelet engraftment**[31]: median 13 days (range 10 to 18)			
				Primary Clinical Effectiveness	Chimerism	Patients followed up to May 2017. Median follow-up not reported At 20 days post-transplant • 5/8 (63%) had 100% donor chimerism • 3/8 (37%) had donor chimerism between 97.8% and 99.6%			

[31] Not further defined. Median calculated by SPH from individual patient data reported by study authors

Use of allogeneic HSCT for PID (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[32]	Patients followed up to May 2017. Median follow-up not reported **Acute GvHD** • Grade I: 1/8 (13%) • Grade III: 1/8 (13%) No patients had grade II or IV GvHD			
Leiding et al 2018	S2 Retrospective case series. The 4 adult patients were treated at centres in Japan, Spain, and Turkey Year of treatment not reported	n=4 Adults with GOF-STAT1 mutations with severe clinical manifestations, including recurrent infections, autoimmunity, IPEX-like symptoms refractory to medical therapy, HLH and CID Median age at HSCT: 29 years[33] (range 18 to 33)	Allogeneic HSCT	Primary Clinical Effectiveness	Post-transplant infection	Median follow-up not reported 2/4 patients (50%) had post-transplant infections which included (number of cases): • Pneumonia: 1 • CMV: 1 • Sepsis: 1[34] • Candidiasis: 1	5	Direct	This uncontrolled retrospective review included a very small number of adult patients from centres in 3 different countries. The time period over which treatment was conducted was not reported. Median follow-up was not reported This study also included data for 11 children. Only the results for the 4 adult patients are extracted here The study authors report that none of these patients had elective HSCT, instead transplantation was intended to be lifesaving to reverse severe infections, HLH or auto-immunity The retrospective design of the study introduces the possibility of selection bias in the study population, e.g. from the completeness or classification of details from patient records As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments
				Primary Clinical Effectiveness	Engraftment	Median follow-up not reported 2/4 patients (50%) had secondary graft loss **Time to neutrophil engraftment** (>500 cells/μL for 3 consecutive days): 3/4 patients (75%) had engraftment at a median of 23 days[33]			

[32] Grading scale not specified but consistent with the modified Glucksberg criteria for acute GvHD (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)

[33] Median calculated by SPH from individual patient data reported by study authors

[34] A second patient had sepsis included as a cause of death, but sepsis was not included as a transplant-related complication for this patient

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						(range 17 to 25)			
				Primary Safety	Mortality[35]	Median follow-up not reported 4/4 patients (100%)			
				Primary Safety	Graft-versus-host disease[36]	Median follow-up not reported **Acute GvHD:** • Grade I: 1/4 (25%) No adult patients had grade II, III or IV GvHD			
				Primary Safety	Transplant-related complications (non-infectious)	Median follow-up not reported 3/4 (75%) had non-infectious complications These included (number of cases): • Severe transfusion-dependent thrombocytopenia: 2 • Reaction to almetuzumab (drug): 1 • Cardiomyopathy and heart failure secondary to cyclophosphamide (drug): 1 • Lymphopenia: 1			

[35] The study authors did not specify whether these deaths were transplant-related

[36] Grading scale not specified but consistent with the modified Glucksberg criteria for acute GvHD (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• Hypogammaglobulinemia: 1			
Partaet al 2017	P1 Prospective case series of patients treated at 1 US centre between 2007 and 2015	n=17 Adults with CGD and sufficient[37] complication from CGD to warrant transplant Median age at HSCT: 24 years (range 18 to 32)	Allogeneic HSCT	Primary Clinical Effectiveness	Overall survival	Median follow-up: 2 years (range 90 days to 5.7 years) 14/17 (82%) alive at follow-up	4	Direct	The design of this small, uncontrolled study was not clearly reported. The study was described as a prospective trial in the study title but no information was provided on the collection/source of data on outcomes. Patients were treated at 1 US centre over an 8 year period This study also included data for 23 children. Only the results relating to the 17 adult patients are extracted here Median age at HSCT and median follow-up were calculated by the SPH reviewer from individual patient data reported by the study authors. Median follow-up was relatively short at 2 years The risk of bias is unclear due to the lack of details about study design As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments
				Primary Clinical Effectiveness	Event-free survival	Median follow-up: 2 years (range 90 days to 5.7 years) 12/17 (71%) event-free at follow-up			
				Primary Clinical Effectiveness	Engraftment	Median follow-up: 2 years (range 90 days to 5.7 years) 3/17 (18%) had graft failure (2 primary graft failure and 1 secondary graft failure[38])			
Shahet al 2017	P1 Case series of patients prospectively enrolled. Number and country of treatment centres	n=5 Adults with DOCK8 PID with ≥1 life-threatening infections, a viral-driven lymphoma or squamous cell carcinoma and	Allogeneic HSCT	Primary Clinical Effectiveness	Overall survival	Median follow-up: 20.9 months (range 5.5 to 31.7) 4/5 (80%) were alive at follow-up	3	Direct	The design of this uncontrolled study was not clearly reported. The patients were described as being prospectively enrolled but no information was provided on the collection/source of data on outcomes. The included a very small number of adult patients. The number of study centres and year of treatment was not reported This study also included data for 2 children. Only the results for the 5 adult patients are extracted here Median age at HSCT and median follow-up were calculated by the reviewer from individual patient data reported by the study authors. Median follow-up
				Primary Clinical Effectiveness	Post-transplant infection	Median follow-up: 20.9 months (range 5.5 to 31.7) 5/5 (100%) had infections after HSCT which included (number of cases):			

[37] Not further defined
[38] Patients with primary graft failure did not engraft after first transplantation. Patients with secondary graft failure had failure after initial engraftment

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	not reported. Years of treatment not reported	adequate organ function Median age at HSCT: 20 years (range 18 to 25)				• CMV reactivation: 4 • BK viraemia: 1 • BK viruria with cystitis: 1 • BK cystitis: 1 • BK haemorrhagic cystitis: 1 • HHV6 viraemia and CSF without clinical sequelae: 1 Adenoviraemia: 1			was relatively short at 20.9 months The risk of bias is unclear due to the lack of details about study design As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments
				Primary Clinical Effectiveness	Engraftment	Median follow-up: 20.9 months (range 5.5 to 31.7) All patients attained engraftment (i.e. no graft failures) **Time to neutrophil engraftment** (>0.5 x 10^9/L for 3 consecutive days): median 15 days (range 13 to 18) **Time to platelet engraftment** (>20 x 10^9/L for 7 consecutive days): median 21 days (range 14 to 35)			
				Primary Clinical Effectiveness	Chimerism	Median follow-up: 20.9 months (range 5.5 to 31.7) **Chimerism at 30 days post-transplant (myeloid; $CD3^+$, NK)** • 4/5 (80%) had 100% donor chimerism			

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						• 1/5 (20%) had 98% to 99% donor chimerism **Chimerism at >100 days post-transplant (myeloid; CD3^{+}, CD19^{+}, NK)** • 4/4 surviving patients (100%) had 100% donor chimerism			
				Primary Safety	Graft-versus-host disease	Median follow-up: 20.9 months (range 5.5 to 31.7) **Acute GvHD[39]:** • Grade I: 1/5 (20%) • Grade II: 2/5 (40%) • Grade III: 1/5 (20%) No patients had grade IV GvHD No patients had chronic GvHD			
Fu et al 2016	S2 Retrospective case series of patients treated at 1 centre in	n=4 Adults and adolescents with HLH PID Median age at HSCT: 23 years (range	Allogeneic HSCT	Primary Clinical Effectiveness	Overall survival	Median follow-up for PID patients not reported At 2 years: 4/4 (100%) 95%CI not reported	5	Direct	This uncontrolled retrospective review included a very small number of adult and adolescent patients from 1 centre in China treated over an 8 year period. Median follow-up was not reported The lower age range of the study population was 14 years old. The proportion of patients aged <18 years was not reported The study also includes data for 26 patients with
				Primary Clinical	Event-free survival	Median follow-up for PID patients not reported			

[39] Grading scale not specified but consistent with the modified Glucksberg criteria for acute GvHD (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	China between 2006 and 2014	14 to 52)		Effectiveness		At 2 years: 4/4 (100%) 95%CI not reported			secondary immunodeficiency[40] or unknown underlying disease which are out of scope of this review. Only data for PID patients are extracted for this review The retrospective design of the study introduces the possibility of selection bias in the study population, e.g. from the completeness or classification of details from patient records As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments
				Primary Clinical Effectiveness	Post-transplant infection	Median follow-up for PID patients not reported Infections reported included (number of cases): • Severe bacterial infection: 1 • Fungal infection: 2 • CMV viremia 1			
				Primary Clinical Effectiveness	Engraftment	Median follow-up for PID patients not reported No patients had graft failure **Time to neutrophil engraftment** (>0.5 x 10^9/L for 3 consecutive days): median 12 days (range 10 to 14) **Time to platelet engraftment** (>20 x 10^9/L for 7 consecutive days): median 13 days (range 11 to 25)			
				Primary Clinical Effectiveness	Chimerism	Median follow-up for PID patients not reported No patients had mixed chimerism (>5% donor			

[40] Secondary HLH is a reactive disorder resulting from e.g. infection, tumour and autoimmune disease

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						cells)			
				Primary Safety	Graft-versus-host disease	Median follow-up for PID patients not reported **Acute GvHD[41]:** No patients had grade II to IV acute GvHD No details on grade I GvHD reported **Chronic GvHD:** 2/4 patients (50%) had localised[42] chronic GvHD No patients had generalised[42] chronic GvHD			
				Primary Safety	Transplant-related complications (non-infectious)	Median follow-up for PID patients not reported Complications reported included (number of cases): • Gastrointestinal haemorrhage: 2			
Oshima et al 2015	S2 Retrospective case series of	n=5 Adults with XLT WAS PID	Allogeneic HSCT	Primary Clinical Effectiveness	Overall survival	Median follow-up: 50 months (range 9 to 144) 4/5 (80%) were alive at follow-up	5	Direct	This uncontrolled retrospective review included a very small number of adult patients from centres in 14 different countries treated over a17 year period This study also included data for 19 children. Only the results for the 5 adult patients are extracted here

[41] Grading scale not specified but consistent with the modified Glucksberg criteria for acute GvHD (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)
[42] Not further defined

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	patients treated at 14 centres[43] in the US, Italy, Germany, Canada and Japan between 1995 and 2012	Median age at HSCT: 20 years (range 19 to 37)		Primary Clinical Effectiveness	Post-transplant infection	Median follow-up: 50 months (range 9 to 144) Infections reported included (number of cases): Pneumococcal pneumonia: 1			Median age at HSCT and median follow-up were calculated by the SPH reviewer from individual patient data reported by the study authors The retrospective design of the study introduces the possibility of selection bias in the study population, e.g. from the completeness or classification of details from patient records As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments
				Primary Clinical Effectiveness	Engraftment	Median follow-up: 50 months (range 9 to 144) All patients achieved engraftment[44]			
				Primary Clinical Effectiveness	Chimerism	Median follow-up: 50 months (range 9 to 144) • 4/5 patients (80%) had 100% donor chimerism • 1/5 patients (20%) had 99.8% donor chimerism			
				Primary Safety	Graft-versus-host disease	Median follow-up: 50 months (range 9 to 144) **Acute GvHD[45]:** • Grade I: 1/5 (20%) • Grade II: 1/5 (20%) No patients had grade III or IV GvHD			

[43] The study included patients from 14 centres. The treatment centres for the 5 adult patients was not reported
[44] Not further defined
[45] Grading scale not specified but consistent with the modified Glucksberg criteria for acute GvHD (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Chronic GvHD: 3/5 patients (60%) had extensive[46] chronic GvHD that was resolved at last follow-up			
Wehr et al 2015	S2 Retrospective case series of patients treated at 14 centres worldwide between 1993 and 2012[47]	n=14 Adults with CVID Median age at HSCT: 34 years (range 18 to 50)	Allogeneic HSCT	Primary Clinical Effectiveness	Overall survival	Median follow-up for adults not reported 8/14 (57%) were alive at follow-up	5	Direct	This uncontrolled retrospective review included limited details about a small number of adult patients from centres in 14 different countries treated over a19 year period. Median follow-up was not reported This study also included data for 11 children. Only the results for the 14 adult patients are extracted here Median age at HSCT was calculated by the SPH reviewer from individual patient data reported by the study authors The retrospective design of the study introduces the possibility of selection bias in the study population, e.g. from the completeness or classification of details from patient records As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments
				Primary Clinical Effectiveness	Engraftment	Median follow-up for adults not reported 3/14 (21%) had graft failure (1 primary graft failure and 2 secondary graft failure)			
				Primary Safety	Graft-versus-host disease[48] Severe GvHD defined as grade III-IV acute GvHD or extensive chronic GvHD	Median follow-up for adults not reported 3/14 (21%) had severe GvHD			
Grossman et al 2014	Study design not reported Uncontrolled study.	n=14 Adults/adolescents with GATA2 deficiency PID and ≥2 episodes of	Allogeneic HSCT	Primary Clinical Effectiveness	Overall survival	Median follow-up: 3.5 years (1 to 5) 8/14 patients (57%) were alive at follow-up	3	Direct	The design of this small, uncontrolled study was not clearly reported. No information was provided on the recruitment of participants or the collection/source of data on outcomes. The number of study centres and year of treatment was not reported Outcomes included data for 1 patient who was <18 years old at HSCT
				Primary Clinical	Post-transplant infection	Median follow-up: 3.5 years (1 to 5)			

[46] Not further defined
[47] The study included patients from 14 centres. The treatment centres and year of treatment for the 14 adult patients was not reported
[48] Grading scale not specified but consistent with the modified Glucksberg criteria for acute GvHD (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	Number and location of treatment centres not reported. Year of treatment not reported	life-threatening opportunistic infections Median age at HSCT: 33 years (range 15 to 46)		Effectiveness		9/14 patients (65%) had post-transplant infections Infections reported included (number of cases): • Invasive fungal infection: 3 • CMV: 3 • Blood stream infection: 3 • Sepsis: 2 • Febrile neutropenia: 1 • Endocarditis: 1 • Acute respiratory distress syndrome: 1 • Gastroenteritis: 1			The risk of bias is unclear due to the lack of details about study design As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments
				Primary Clinical Effectiveness	Engraftment[49]	Median follow-up: 3.5 years (1 to 5) **Time to neutrophil engraftment** (>0.5 x 10^9/L for 3 consecutive days): • MRD/URD (n=8): median 12 days (range 0 to 13) • UCB (n=3[50]): median not reported (range 16 to 80 days) • Haplo (n=1): 19 days[51]			

[49] Outcome not available for the study cohort as a whole. Breakdown of outcomes reported as presented by the study authors
[50] A fourth patient did not have evaluable data
[51] A second patient died soon after transplantation

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Time to platelet engraftment (>20 x 10^9/L for 7 consecutive days): • MRD (n=4): median 16 days (range 0 to 18) • URD (n=4): median 13 days (range 0 to 18) • UCB (n=2[52]): 32 and 302 days • Haplo (n=1): platelet engraftment not achieved			
				Primary Clinical Effectiveness	Chimerism	Median follow-up: 3.5 years (1 to 5) For evaluable patients (who initially engrafted) (n not reported) **At 100 days post-transplant:** • Myeloid cells: All patients 100% donor cells • CD14+ monocytes, CD3-/CD56+ NK cells: 98%to100% • CD3+: median 91% (range 29 to 100) **At 12 months post-transplant:** • Myeloid cells: All			

[52] 2 further patients did not have evaluable data

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						98% to100% donor cells • CD14+ monocytes, CD3-/CD56+ NK cells: 98% to100% donor cells • CD3+: median 93% (range 65 to 100)			
				Primary Safety	Graft-versus-host disease Chronic GvHD defied according to National Institutes of Health criteria for severity[53]	Median follow-up: 3.5 years (1 to 5) **Acute GvHD[54]:** • Grade I-II: 5/14 (36%) • Grade III: 1/14 (7%) • Grade IV: 2/14 (14%) **Chronic GvHD:** • Mild: 2/14 (14%) • Severe: 1/14 (7%)			
Güngör et al 2014	P1 Prospective case series of patients treated at 16 centres worldwide between	n=13 Adults with CGD offered reduced intensity conditioning [55] There were no pre-specified inclusion/	Allogeneic HSCT	Primary Clinical Effectiveness	Overall survival	Median follow-up for adults not reported. Minimum follow-up was 6 months 12/13 (92%) were alive at follow-up	5	Direct	This uncontrolled prospective study included a small number of adult patients from centres in 16 different countries treated over a 9 year period. Median follow-up was not reported This study also included data for 43 children. Only the results relating to the 13 adult patients are extracted here Median age at HSCT was calculated by the SPH reviewer from individual patient data reported by the study authors
				Primary Clinical Effectiveness	Post-transplant infections	Median follow-up for adults not reported. Minimum follow-up was 6 months			

[53] Graded as mild; moderate; severe (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)
[54] Grading scale not specified but consistent with the modified Glucksberg criteria for acute GvHD (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)
[55] Regimen designed to enhance myeloid engraftment and reduce organ toxicity in patients with mainly high-risk CGD

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	2003 and 2012	exclusion criteria Median age at HSCT: 21.4 years (range 18.5 to 39.3)				4/13 (31%) had a post-transplant infection, including (number of cases): • Cholecystitis: 1 • Rotavirus infection: 1 • CMV reactivation: 1 • EBV reactivation: 1			A prospective design should reduce the possibility of selection bias, however in this study there were no pre-specified inclusion/ exclusion criteria and enrolment was at the discretion of individual centres. The risk of bias is unclear As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments
				Primary Clinical Effectiveness	Engraftment	Median follow-up for adults not reported. Minimum follow-up was 6 months 1/13 (8%) had secondary graft failure			
				Primary Clinical Effectiveness	Chimerism	Median follow-up for adults not reported. Minimum follow-up was 6 months **Myeloid chimerism** • 100% donor cells: 9/13 (69%) • 97-98% donor cells: 3 (23%) • Graft failure: 1 (8%)			
				Primary Clinical Effectiveness	Immunosuppressants	Median follow-up for adults not reported. Minimum follow-up was 6 months All surviving patients (n=12) off immunosuppressants at last follow-up			
				Primary Safety	Graft-versus-host disease	Median follow-up for adults not reported. Minimum follow-up was			

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
					Chronic GvHD defied according to National Institutes of Health criteria for severity[56]	6 months **Acute GvHD[57]:** • Grade I: 5/13 (38%) • Grade II: 2/13 (15%) No patients had grade III or IV GvHD **Chronic GvHD** 1/13 patients (8%) developed chronic GvHD			
				Primary Safety	Transplant-related complications (non-infectious)	Median follow-up for adults not reported. Minimum follow-up was 6 months 6/13 (46%) had transplant-related complications. These included (number of cases): • Renal insufficiency, early cessation of ciclosporin: 1 • Transient red-cell aplasia: 3 • Pulmonary and gastrointestinal deterioration: 1 • Nephrotic syndrome: 1			

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

[57] Grading scale not specified but consistent with the modified Glucksberg criteria for acute GvHD (https://www.england.nhs.uk/wp-content/uploads/2017/03/gvhd-heamatopoietic-stem-cell.pdf)

Use of allogeneic HSCT for PID (no comparator)									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Spinner et al 2014	S2 Retrospective case series of patients treated at 1 US centre between 1992 and 2013	n=21 Adults/adolescents with GATA2 deficiency who underwent HSCT for MDS/AML, PAP and/or recurrent infection Age at HSCT: 15 to 49 years (median not reported)	Allogeneic HSCT	Primary Clinical Effectiveness	Overall survival	Median follow-up 14 months (range 0 to 180) • At 1 year: 72% • At 2 years: 65% • At 4 years: 54% 95%CI only reported graphically	5	Direct	This uncontrolled retrospective review included limited details on outcomes about a small number of adult patients who received HSCT at 1 US centre over a 21 year period The primary focus of this study was to characterise GATA2 deficiency and explore genotype-phenotype associations. This is outside the scope of this review The study included 57 patients in total, with 21 receiving HSCT. The age range of the patients receiving HSCT was reported and these were adults of adolescents. The age range of the whole population is wider (5 months to 78 years). Therefore outcomes for the whole study population and non-HSCT population are not reproduced. Only details of the outcomes for patients who received HSCT are extracted Median follow-up was relatively short at 14 months The retrospective design of the study introduces the possibility of selection bias in the study population, e.g. from the completeness or classification of details from patient records As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments

AML – acute myeloid leukaemia; CGD – chronic granulomatous disease; CID – combined immunodeficiency; CMV – cytomegalovirus; CVID – common variable immunodeficiency; DOCK8 – dedicator-of-cytokinesis 8; EBV – Epstein Barr virus; GOF – gain-of-function; GvHD – graft-versus-host disease; haplo – haploidentical related donor; HCT-CI – haematopoietic cell transplantation – comorbidity index; HLH – haemophagocytic lymphohistiocytosis; HSCT – haematopoietic stem cell transplantation; IPEX – immune dysregulation-polyendocrinopathy-enteropathy-X-linked; IQR – interquartile range; IVIG – intravenous immunoglobulin; L – litres; MDS – familial myelodysplastic syndromes; MRD – matched related donor; PAP – pulmonary alveolar proteinosis; PID – primary immunodeficiencies; STAT1 – signal transducer and activator of transcription 1; UCB – umbilical cord blood donor; UK – United Kingdom; URD – matched unrelated donor; US – United States; XLT – X-linked thrombocytopenia

8 Grade of Evidence Table

For abbreviations see list after each table

Use of allogeneic HSCT for PID (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall survival	Albert et al (2018)	6	Direct	B	Overall survival is the time from transplant to death from any cause. In a recent UK study with the largest sample size (Fox et al 2018) overall survival was 89% at 1 year and 85% at 3 years (no confidence intervals reported) in adults with a variety of PIDs who had developed complications that necessitated definitive treatment with curative intent (i.e. HSCT). Mean follow-up was 3.5 years. Overall survival was high. 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 a 12 year period to 2016. The study does not include a comparison with any alternative treatment strategy. The 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.
	Fox et al (2018)	6	Direct		
	Jin et al (2018)	5	Direct		
	Parta et al (2017)	4	Direct		
	Shah et al (2017)	3	Direct		
	Fu et al (2016)	5	Direct		
	Oshima et al (2015)	5	Direct		
	Wehr et al (2015)	5	Direct		
	Grossman et al (2014)	3	Direct		
	Güngör et al (2014)	5	Direct		
	Spinner et al (2014)	5	Direct		
Event-free survival	Albert et al (2018)	6	Direct	B	Event-free survival is the time from transplant to graft failure, graft rejection or death from any cause. In a recent UK study with the largest sample size (Fox et al 2018) event-free survival was 90% at both 1 and 3 years (no confidence intervals reported) in adults with a variety of PIDs who had developed complications that necessitated definitive treatment with curative intent (i.e. HSCT). Mean follow-up was 3.5 years. Event-free survival was high. A high event-free 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 a 12 year period to 2016. The study does not include a comparison with any alternative treatment strategy. The 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.
	Fox et al (2018)	6	Direct		
	Parta et al (2017)	4	Direct		
	Fu et al (2016)	5	Direct		

Use of allogeneic HSCT for PID (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Post-transplant infection	Fox et al (2018)	6	Direct	B	Post-transplant infection relates to the infections experienced by patients after transplantation. In a recent UK study with the largest sample size (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 of the high proportion of infections is unclear. This small, uncontrolled retrospective study included 29 patients who received HSCT at 2 UK centres over a 12 year period to 2016. The study does not include a comparison with any alternative treatment strategy. The mean follow-up was relatively short at 3.5 years. The retrospective design introduces the possibility of selection bias and the lack of comparator limits the strength of the conclusions that can be drawn.
	Jin et al (2018)	5	Direct		
	Leiding et al 2018	5	Direct		
	Shah et al (2017)	3	Direct		
	Fu et al (2016)	5	Direct		
	Oshima et al (2015)	5	Direct		
	Grossman et al (2014)	3	Direct		
	Güngör et al (2014)	5	Direct		
Engraftment	Albert et al (2018)	6	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: graft failures or rejections[58]; time to neutrophil engraftment (defined by Fox et al (2018) as ≥0.5 x 10^9/L) and time to platelet engraftment (defined by Fox et al (2018) as ≥50 x 10^9/L). In a recent UK study with the largest sample size (Fox et al 2018) there were no graft failures or rejections. The median time to neutrophil engraftment was 12 days (IQR 11 to 17) and the median time to platelet engraftment was 14 days (IQR 11 to 20). Engraftment is a positive outcome of HSCT implying that the patient is successfully producing new blood and immune cells. This small, uncontrolled retrospective study included 29 patients who received HSCT at 2 UK centres over a 12 year period to 2016. The study does not include a comparison with any alternative treatment strategy. The mean follow-up was relatively short at 3.5 years. The retrospective design introduces the possibility of selection bias and the lack of comparator limits the strength of the conclusions that can be drawn.
	Fox et al (2018)	6	Direct		
	Jin et al (2018)	5	Direct		
	Leiding et al 2018	5	Direct		
	Parta et al (2017)	4	Direct		
	Shah et al (2017)	3	Direct		
	Fu et al (2016)	5	Direct		
	Oshima et al (2015)	5	Direct		
	Wehr et al (2015)	5	Direct		
	Grossman et al (2014)	3	Direct		
	Güngör et al (2014)	5	Direct		
Chimerism	Albert et al (2018)	6	Direct	B	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 specific lineages i.e. for peripheral blood mononuclear cells, T-cells, B-cells and granulocyte compartments or across multiple lineages. In a recent UK study with the largest sample size (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.
	Fox et al (2018)	6	Direct		
	Jin et al (2018)	5	Direct		
	Shah et al (2017)	3	Direct		
	Fu et al (2016)	5	Direct		
	Oshima et al (2015)	5	Direct		

[58] Not further defined

Use of allogeneic HSCT for PID (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
	Grossman et al (2014)	3	Direct		Full donor chimerism is a positive outcome of HSCT. 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. This small, uncontrolled retrospective study included 29 patients who received HSCT at 2 UK centres over a 12 year period to 2016. The study does not include a comparison with any alternative treatment strategy. The mean follow-up was relatively short at 3.5 years. The retrospective design introduces the possibility of selection bias and the lack of comparator limits the strength of the conclusions that can be drawn.
	Güngör et al (2014)	5	Direct		
Immune reconstitution	Albert et al (2018)	6	Direct	B	Immune reconstitution relates to the recovery of the immune system. Outcomes reported included continued requirement for monthly immune replacement and receipt of immunosuppression post-transplant. In a recent UK study with the largest sample size (Fox et al 2018) monthly immune replacement had ceased in 89% of the 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 of HSCT, implying recovery of the immune system which is likely to have a positive impact on quality of life. This small, uncontrolled retrospective study included 29 patients who received HSCT at 2 UK centres over a 12 year period to 2016. The study does not include a comparison with any alternative treatment strategy. The mean follow-up was relatively short at 3.5 years. The retrospective design introduces the possibility of selection bias and the lack of comparator limits the strength of the conclusions that can be drawn.
	Fox et al (2018)	6	Direct		
	Güngör et al (2014)	5	Direct		
Transplant-related mortality	Albert et al (2018)	6	Direct	B	Transplant-related mortality is death from causes related to the transplant. In a recent UK study with the largest sample size (Fox et al 2018) transplant-related mortality was 14% (4 patients). The cause of death for 2 of the 4 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 to be low by the study authors, reflecting the seriousness of PID and the risks associated with HSCT. A low transplant-related mortality 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 a 12 year period to 2016. The study does not include a comparison with any alternative treatment strategy. The mean follow-up was relatively short at 3.5 years. The retrospective design introduces the possibility of selection bias and the lack of comparator limits the strength of the conclusions that can be drawn.
	Fox et al (2018)	6	Direct		
	Leiding et al 2018[59]	5	Direct		

[59] The study authors did not specify whether these deaths were transplant-related

Use of allogeneic HSCT for PID (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Graft-versus-host disease	Albert et al (2018)	6	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 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[60]. In a recent UK study with the largest sample size (Fox et al 2018) 45% of 29 patients had acute GvHD. This consisted of 28% of patients 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. This small, uncontrolled retrospective study included 29 patients who received HSCT at 2 UK centres over a 12 year period to 2016. The study does not include a comparison with any alternative treatment strategy. The mean follow-up was relatively short at 3.5 years. The retrospective design introduces the possibility of selection bias and the lack of comparator limits the strength of the conclusions that can be drawn.
	Fox et al (2018)	6	Direct		
	Jin et al (2018)	5	Direct		
	Leiding et al 2018	5	Direct		
	Shah et al (2017)	3	Direct		
	Fu et al (2016)	5	Direct		
	Oshima et al (2015)	5	Direct		
	Wehr et al (2015)	5	Direct		
	Grossman et al (2014)	3	Direct		
	Güngör et al (2014)	5	Direct		
Transplant-related complications (non-infectious)	Fox et al (2018)	6	Direct	B	Transplant-related complications relates to non-infectious complications experienced after transplant. In a recent UK study with the largest sample size (Fox et al 2018) 69% of 29 patients had post-transplant complications. Complications experienced by more than one 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 transplantation can be life threatening. No grading system was used to specify the seriousness of the complications reported so the clinical meaningfulness of the high proportion of complications is unclear. This small, uncontrolled retrospective study included 29 patients who received HSCT at 2 UK centres over a 12 year period to 2016. The study does not include a comparison with any alternative treatment strategy. The mean follow-up was relatively short at 3.5 years. The retrospective design introduces the possibility of selection bias and the lack of comparator limits the strength of the conclusions that can be drawn.
	Leiding et al 2018	5	Direct		
	Fu et al (2016)	5	Direct		
	Güngör et al (2014)	5	Direct		

CMV – cytomegalovirus; EBV – Epstein Barr virus; GvHD – graft-versus -host disease; HSCT – haematopoietic stem cell transplantation; IQR – interquartile range; L – litres; PID – primary immunodeficiencies; UK – United Kingdom

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

9 Literature Search Terms

<table>
<tr><th colspan="2">Search strategy</th></tr>
<tr><td>P – Patients / Population
Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?</td><td>Adult patients with primary immunodeficiencies

[Suggest combine the words “transplant” “adult” “diagnosis (abbreviated and in full) as listed below:

• CGD, Chronic Granulomatous Disease
• CD40 Ligand Deficiency
• Hyper IgM, Hyper IgM syndrome
• WAS, Wiskott Aldrich Syndrome
• HLH, haemophagocytic lymphohistiocytosis
• CTLA4, CTLA4 deficiency, cytotoxic T-lymphocyte-associated protein 4;
• XIAP, XIAP deficiency, X-linked inhibitor of apoptosis protein
• CVID, Common variable immune deficiency
• RAG, recombination activating gene Immunodeficiency
• CID, Combined Immunodeficiency
• Immune deficiency or Immunodeficiency]</td></tr>
<tr><td>I – Intervention
Which intervention, treatment or approach should be used?</td><td>Allogeneic haematopoietic stem cell transplant (HSCT) – many different terms are used as illustrated below.

[Suggest use “transplant” for search purposes:
• Allogenic/Allogeneic/Allo
• Hematopoietic/Hemopoietic/Haematopoeitic/Haemopoietic/HSCT)]</td></tr>
<tr><td>C – Comparison
What is/are the main alternative/s to compare with the intervention being considered?</td><td>Conservative non-transplant therapy, including one or more of:
• antimicrobial therapy,
• therapy with antibodies,
• biological modifying drugs (e.g., interferon, gamma interferon),
• immunoglobulin (IVIG) replacement therapy,
• systemic immunosuppressive therapy (for auto-inflammatory/immune dysregulation complications)</td></tr>
<tr><td>O – Outcomes
What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.</td><td>All outcome measures reported in included studies

<u>Critical to decision-making:</u>
• Survival
• Infection rates
• Time to relapse/relapse rate – relapses will include infection/malignancy/inflammation/autoimmunity
• Clinical response
• Safety / adverse events
• Cost effectiveness
• Quality of life
• Health care utilisation/number of hospital visits (outpatient and inpatient)

<u>Important to decision-making:</u>
Compliance with treatment</td></tr>
<tr><td colspan="2">Assumptions / limits applied to search
<u>Inclusion criteria:</u>
Peer-reviewed publications in the English language
2008 to present
Randomised studies, non-randomised prospective cohort studies, case-control studies, case series

<u>Exclusion criteria:</u>
Case reports</td></tr>
</table>

10 Search Strategy

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

Search date: 16th August 2018
Embase search:

1 exp bone marrow transplantation/
2 allotransplantation/
3 ((H?ematopoietic or Stem Cell or bone marrow or allo* or auto*) adj3 (transplant* or allotransplant*)).ti,ab.
4 (hct or hsct or allohct or allohsct or autohct or autohsct or bmt).ti,ab.
5 transplant*.ti.
6 1 or 2 or 3 or 4 or 5
7 combined immunodeficiency/ or common variable immunodeficiency/ or exp severe combined immunodeficiency/ or wiskott aldrich syndrome/
8 ((primary or innate or inherited) adj (immun?deficienc* or immun* deficienc*)).ti,ab.
9 ((combined or adenosine deaminase or common variable) adj (immun?deficienc* or immun* deficienc*)).ti,ab.
10 ((recombinant or recombination) adj activating gene*).ti,ab.
11 wiskott aldrich syndrome?.ti,ab.
12 (hyper igm or hyper ige).ti,ab.
13 ((ligand or ctla4 or cytotoxic t-lymphocyte* or xiap or x-linked inhibitor or iap3 or birca4 or antibod*) adj3 deficien*).ti,ab.
14 (chronic granulomatous adj (disease? or disorder?)).ti,ab.
15 ((hemophagocytic or haemophagocytic) adj lymphohistiocytosis).ti,ab.
16 (phagocytic cell adj (disease or disorder?)).ti,ab.
17 ((cd40 or cd-40 or cd152 or cd152) adj3 deficien*).ti,ab.
18 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 6 and 18
20 (exp animals/ or nonhuman/) not human/
21 19 not 20
22 (conference* or editorial or letter or note or "review").pt. or case report/
23 21 not 22
24 limit 19 to "reviews (maximizes specificity)"
25 23 or 24
26 limit 25 to (english language and yr="2008 -Current")

11 Evidence Selection

- Total number of publications reviewed: 148
- Total number of publications considered potentially relevant[61]: 71
- Total number of publications selected for inclusion in this briefing: 12

References from the PWG supplied in the PPP	Paper selection decision and rationale if excluded
1. Güngör, T., Teira, P., Slatter, M., Stussi, G., Stepensky, P., Moshous, D., Vermont, C., Ahmad, I., Shaw, P., da Cunha, J., Schlegel, P., Hough, R., Fasth, A., Kentouche, K., Gruhn, B., Fernandes, J., Lachance, S., Bredius, R., Resnick, I., Belohradsky, B., Gennery, A., Fischer, A., Gaspar, H., Schanz, U., Seger, R., Rentsch, K., Veys, P., Haddad, E., Albert, M. and Hassan, M. (2014). Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study. The Lancet, 383(9915), pp.436-448	Included in the review (adult patients)
2. Ozsahin, H., Cavazzana-Calvo, M., Notarangelo, L., Schulz, A., Thrasher, A., Mazzolari, E., Slatter, M., Le Deist, F., Blanche, S., Veys, P., Fasth, A., Bredius, R., Sedlacek, P., Wulffraat, N., Ortega, J., Heilmann, C., O'Meara, A., Wachowiak, J., Kalwak, K., Matthes-Martin, S., Gungor, T., Ikinciogullari, A., Landais, P., Cant, A., Friedrich, W. and Fischer, A. (2007). Long-term outcome following hematopoietic stem-cell transplantation in Wiskott-Aldrich syndrome: collaborative study of the European Society for Immunodeficiencies and European Group for Blood and Marrow Transplantation. Blood, 111(1), pp.439-445	Excluded because all patients were <18 years old at the time of transplantation
3. Pai, S., Logan, B., Griffith, L., Buckley, R., Parrott, R., Dvorak, C., Kapoor, N., Hanson, I., Filipovich, A., Jyonouchi, S., Sullivan, K., Small, T., Burroughs, L., Skoda-Smith, S., Haight, A., Grizzle, A., Pulsipher, M., Chan, K., Fuleihan, R., Haddad, E., Loechelt, B., Aquino, V., Gillio, A., Davis, J., Knutsen, A., Smith, A., Moore, T., Schroeder, M., Goldman, F., Connelly, J., Porteus, M., Xiang, Q., Shearer, W., Fleisher, T., Kohn, D., Puck, J., Notarangelo, L., Cowan, M. and O'Reilly, R. (2014). Transplantation Outcomes for Severe Combined Immunodeficiency, 2000–2009. New England Journal of Medicine, 371(5), pp.434-446	Excluded because all patients were <18 years old at the time of transplantation

12 References

Albert MH. Hauck F. Wiebking V. Aydin S. Notheis G. Koletzko S. Führer M. Tischer J. Klein C. Schmid I. Allogeneic stem cell transplantation in adolescents and young adults with primary immunodeficiencies. *J Allergy Clin. Immunol. Pract. 6(1): 298-301*.

Fox TA. Chakraverty R. Burns S. Carpenter B. Thomson K. Lowe D. Fielding A. Peggs K. Kottardis P. Uttenthal B. Bigley V. Buckland M. Grandage V. Denovan S. Grace S. Dahlstrom J. Workman S. Symes A. Mackinnon S. Hough R. Morris E. 2018. Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency. *Blood 131(8): 917-931*.

[61] This includes studies where the age of the patients could not be determined from the abstract

Fu L. Wang J. Wei N. Wu L. Wang Y. Huang W. Zhang J. Liu J. Wang Z. 2016. Allogeneic hematopoietic stem-cell transplantation for adult and adolescent haemophagocytic lymphohistiocytosis: a single center analysis. *Int. J. Hematol 104: 628-635.*

Grossman J. Cuellar-Rodriguez J. Gea-Banacloche J. Zerbe C. Calvo K. Hughes T. Hakim F. Cole K. Parta M. Freeman A. Holland SM. Hickstein DD. 2014. Nonmyeloablative allogeneic hematopoietic stem cell transplantation for GATA2 deficiency. *Biology of Blood and Marrow Transplantation 20: 1940-1948.*

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