NHS England

Evidence review: Allogeneic haematopoietic stem cell transplant for primary immunodeficiencies

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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, in press). 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 (Morris & Veys 2017).
- Nearly 300 distinct immunodeficiencies have been described, with 20 specific diseases accounting for 90% of cases (Fox et al, in press). There are also categories of 'unspecified' and 'other' (Fox et al, in press).
- There are many variations in clinical manifestations (Fox et al, in press). Patients with severe PID may present with serious of 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 (Morris & Veys 2017).
- Untreated PID can lead to ongoing recurrent, progressive or life threatening infection, autoimmunity and malignant disease, resulting in poor quality of life and early death (Morris & Veys 2017).
- Without transplantation there is a high disease burden in adulthood and poor survival (Morris & Veys 2017). Without intervention infants/ children with severe PID do not survive (Morris 2018). As a result, randomised controlled trials are considered unethical (Morris 2018).

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

- We did not identify any NICE guidance on allogeneic haematopoietic stem cell transplant (HSCT).

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 (Morris & Veys, 2017).
- Only a small proportion of PID patients are suitable for and meet the criteria for HSCT (Morris & Veys 2017).
- Between 2013 and 2016, 60-68 people per year received HSCT for PID (Morris & Veys 2017).

Standard treatment and pathway of care

- For children (aged ≤18) with SCID, the current standard treatment is allogeneic HSCT (Morris & Veys 2017). For other types of PID the decision to treat with HSCT is made on an individual basis (Morris & Veys 2017).
- Other treatments might include ongoing antimicrobial therapy, therapy with antibodies, and/or biological modifying drugs (Morris & Veys 2017).
- Commissioning for allogeneic HSCT for adults with PID has recently been agreed on an interim basis via an Urgent Clinical Commissioning Policy Statement (Morris 2018). Prior to this it was occasionally funded via individual funding requests (Morris 2018).

- Standard treatment for adults includes: immunoglobulin 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 all patients with susceptibility to infections (Morris & Veys 2017).

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 (Morris & Veys 2017).
- Sources of stem cell include bone marrow, peripheral blood or cord blood from appropriately matched donors (Morris 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).
- Currently, the only alternative potentially curative therapy is Gene Therapy. However, this uses autologous[2] HSCT with gene corrected stem cells (Morris & Veys 2017). Gene therapy for ADA-SCID is now licensed and therefore available for a small number of patients for whom it is appropriate (Morris 2018).
- Allogeneic HSCT is a high-cost, specialist procedure performed in specialist centres. In the UK, HSCT procedures for children with PID have largely been conducted within two designated highly specialised service centres since 1993 (Morris & Veys 2017).
- Without HSCT patients with primary immunodeficiencies have a high disease burden in adulthood and poor or no survival. The diseases are rare or ultra-rare and heterogeneous. Both these factors limit the availability of RCT evidence or large studies (Morris 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 be a curative treatment (Morris & Veys 2017), resulting in the production of healthy immune cells.
- Allogeneic transplantation has a relatively high mortality and morbidity which must be weighed against the potential for longer-term survival benefits and opportunity for cure of an inherited disease (Morris & Veys 2017).

2 Summary of results

- This evidence review found 16 uncontrolled studies with 100 or more patients. Six of these included patients with any PID and ten focused on one type of PID e.g. SCID or Wiskott-Aldrich syndrome (WAS). Five of the 16 studies included patients who were more than 18 years old at HSCT. No studies compared HSCT with alternative treatment strategies.

[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
[2] Using cells from the same individual

- Survival (15 uncontrolled studies; n=5,043[3]): Survival after HSCT, reported as overall survival or for a fixed term (e.g. five years), ranged from 62% to 90% but was mostly over 70%. Some studies reported survival for sub-groups of patients with rates generally higher for patients who received HSCT in more recent years (e.g. after 2000) or who received genotypically matched donor cells. One study reported nine-year survival for a sub-group of patients who had survived more than two years after HSCT as 92% (confidence intervals not reported). In multivariate analysis common risk factors significantly associated with survival included age at HSCT (favouring younger ages), donor type (favouring matched sibling donors) and infection prior to HSCT (favouring no infection).
- Mortality (three uncontrolled studies; n=847[3]): The cumulative one-year incidence of transplant-related mortality was 22% in one study (n=135; confidence intervals not reported). In multivariate analysis increased risk of transplant-related mortality was significantly associated with active cytomegalovirus disease, interstitial pneumonitis and veno-occlusive disease ($p<0.05$). One study (n=606) reported the excess deaths per 1,000 for HSCT patients two to six years after HSCT as 54 (95%CI 28 to 79) for SCID patients and 38 (95%CI 25 to 51) for non-SCID patients compared to an age, sex and nationality matched general population. In six to ten years after HSCT there was no significant difference in mortality risk for surviving patients compared to the general population (p value not reported).
- Engraftment[4] (eight uncontrolled studies; n=2,189[3]): Engraftment rates ranged from 72% to 96% but was mostly over 80%. Some studies reported neutrophil and platelet engraftment separately with rates ranging from 76% to 89%.
- Chimerism (the presence of donor cells) (three uncontrolled studies; n=683[3]): In one study (n=194) the rate of mixed chimerism[5] 12 months or more after HSCT was 28% (confidence intervals not reported). Donor type affected chimerism with one study reporting that significantly fewer patients from mismatched related donors had full[6] or mixed chimerism (39%) compared to matched sibling donors (80%) or other donors (71%) (n=240; $p<0.001$).
- Immunologic reconstitution (eight uncontrolled studies; n=1,365[3]): Studies reported various T and B lymphocyte outcomes after HSCT; generally reporting normalisation of cell counts of at least 60% of patients. Factors significantly affecting immunologic reconstitution in multivariate analyses were donor type, conditioning regimen, phenotype and presence of chimerism. The proportion of patients that did not require intravenous immunoglobulin (IVIG) at follow-up varied between studies from 14% to 89%. In one multivariate analysis factors significantly increasing long-term requirement for IVIG included the ARTEMIS gene defect, poor T-cell reconstitution, requirement of an additional transplant procedure and HSCT from a haploidentical donor ($p<0.05$). In another multivariate analysis independence from IVIG therapy at two years was significantly associated with donor type (favouring matched siblings), and conditioning regimen (favouring reduced-intensity or myeloablative conditioning) ($p<0.05$).
- Requirement for more than one HSCT (eight uncontrolled studies; n=1,365[3]): The proportion of patients who required more than one HSCT ranged from 9% to 28%.
- Admission to intensive care (one uncontrolled study; n=111): 35% of patients required at least one ICU admission at a median of 31 days after HSCT with the most common reason for admission being respiratory problems (59%). The median duration of admission was six days.

[3] It is possible that the same patients may have been included in more than one of the studies.
[4] 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
[5] A combination of patient and donor cells
[6] All donor cells

- Post-transplant malignancy (one uncontrolled study; n=2,266): 2.3% of patients developed a confirmed post-transplant malignancy. Lymphoproliferative disorders were the most common malignancy (87%) with a median time to development of three months after HSCT.
- Activities of daily living (two uncontrolled studies; n=346) assessed using Karnofsky/ Lanksky scores[7]: One study (n=176) reported that surviving patients treated with HSCT had significantly higher median scores (100%) than patients who did not receive HSCT (90%) at last follow-up (p<0.001). Another study (n=170) reported that for 84% of patients the score did not fall below 100% between two and 14 years after HSCT. A further 13% had a lowest score of 90%.
- Quality of Life (one uncontrolled study; n=111): One study reported that 86% of patients were considered to be healthy by their families with 36% reporting no health problems in the last two years. Where health problems were reported the most common (affecting ≥10%) were persistent rash (25%), sinusitis (20%), asthma (14%), diarrhoea (14%), attention deficit hyperactivity disorder (ADHD) (21%) and developmental delay (10%). 12% of patients were below the 3rd percentile for height and weight and 3% required special schooling.
- Centre assessment of post-HSCT outcome (one uncontrolled study; n=170): 53% of patients were considered 'cured', 18% were considered 'improved', 3% were considered 'unchanged' and 3% were considered 'worse'. For 23% of patients the status was unknown. No definitions were provided for the categories used.
- **Safety** (14 uncontrolled studies; n=5,716[3]): One study (n=124) reported that 67% of deaths were transplant related. The most common cause of death following HSCT was infection accounting for between 20% and 76% of deaths reported by studies. The most common causes of death in patients who did not receive HSCT (reported in one study; n=176) were malignancy and liver failure (both 27%) and infection (23%).
- In one study (n=194) 46% of patients experienced complications in the year after HSCT, with the most common being infection requiring hospitalisation (28%). In multivariate analysis, the only significant risk factor for complications was HSCT from a mismatched family donor compared to a matched sibling donor (p=0.019). Another study (n=145) reported late clinical complications in 49% of patients who had survived more than two years after HSCT with the most common being autoimmune manifestations (24%), severe or recurrent infections (24%) and poor growth (29%). In multivariate analysis the factors significantly associated with late clinical complications included diagnosis of the ARTEMIS gene defect, viral infection prior to HSCT, treatment with alkylator agents, requirement of an additional HSCT procedure and requirement for IVIG (p<0.01).
- The proportion of patients experiencing acute graft versus host disease[8] (GVHD) (grade II to IV) at 100 days ranged from 19% to 25%. The proportion of patients experiencing acute GVHD (grade III to IV) at 100 days was 8%. The proportion of patients experiencing chronic GVHD at one or two years was 15 to 16%. In a multivariate analysis, decreased risk of GVHD was associated with use of a fully matched sibling donor and HSCT performed after 1998 (p=0.002).

[7] Karnofsky/ Lansky scores are used to determine functional status. The Karnofsky Scale is designed for people aged ≥16 years and the Lansky Scale is designed for people <16 years old. Both scales are scored from 10 to 100. Higher scores indicate better function (CIBMTR 2009). 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.

[8] In graft versus host disease (GVHD) the donated cells react against the patient's body which can lead to an immune response attack. GVHD is graded as I – mild; II – moderate; III – severe; IV – life threatening

- **Cost–effectiveness.** No studies assessing the cost-effectiveness of allogeneic HSCT for PID patients were identified.
- Descriptive results from uncontrolled studies provide evidence of generally positive outcomes for surviving patients after HSCT with most studies reporting survival rates of over 70%. However, where reported, approximately half of surviving patients still experienced complications one and two years after HSCT.
- 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 the conclusions that can be drawn.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: PubMed, Embase and Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1st January 2000 and 1st December 2017.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO criteria were then selected for inclusion in this review.
- As a large number of studies meeting the PICO were identified, a cut-off based on study sample size was applied in line with the agreed methodology for conducting NHS England evidence reviews. Therefore only the larger studies with more than 100 patients are included in this review.
- 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

A total of 16 papers matching the PICO were included: all uncontrolled studies with between 100 and 2,266 PID patients. Six of these included patients with any PID and 10 focused on one type of PID e.g. SCID or Wiskott-Aldrich syndrome (WAS). Five of the 16 studies included patients who were more than 18 years old at HSCT. The median follow-up after HSCT varied from 25 months to 11 years. Full details of the study designs and outcomes are summarised in the evidence tables in section 7.

Clinical effectiveness

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

No studies comparing allogeneic HSCT to alternative treatment strategies were identified. The outcomes reported in the uncontrolled studies included survival, mortality, engraftment, chimerism, immunologic reconstitution, requirement for more than one HSCT, admission to intensive care, post-transplant mortality, activities of daily living, quality of life and centre assessment. Due to differences in the patient populations and reporting it is difficult to compare results between studies. Further details of the outcomes reported are provided in the tables in sections 7 and 8.

Survival

Survival outcomes were reported in 15 uncontrolled studies. These were usually reported as overall survival (6 studies) or survival for a fixed term (e.g. between two and nine years in different studies) (10 studies). Confidence intervals around survival outcomes are provided where reported.

Four studies reported survival for patients with more than one form of PID. In Cole et al (2012; n=111) overall survival was 76% and in Mitchell et al (2013; n=135) five-year survival was 72%. In Gennery et al (2010; n=1,482) four-year survival for non-SCID patients was reported by year of HSCT and ranged from 54% (95%CI 49 to 61) prior to 1995 to 69% (95%CI 60 to 78) from 2000-2005 and in Antoine et al (2003; n=919) three-year survival for non-SCID patients was reported by donor type and was 71% for genotypically HLA-matched, 42% for phenotypically HLA-matched, 42% for HLA-mismatched related and 59% for unrelated donor transplant.

For SCID patients, overall survival was 62% (95%CI 52 to 70) (Schuetz et al 2014; n=145), 67% (Hassan et al 2012; n=106) and 77% (Railey et al 2009; n=161). Railey et al (2009) also reported eight-year survival for SCID patients as significantly higher for patients receiving HSCT before 3.5 months old (96%; 95%CI 84 to 99) compared to more than 3.5 months old (70%; 95%CI 60 to 77). Five-year survival was 74% (95%CI 68 to 79) (Pai et al 2014; n=240) and two-year survival was 90% (95%CI 80 to 95) (Heimall et al 2017; n=100). In Gennery et al (2010; n=1,482) five-year survival was reported by year of HSCT and ranged from 56% (95%CI 51 to 62) prior to 1995 to 71% (95%CI 63 to 80) from 2000-2005. In Fernandes et al (2012; n=249) there was no significant difference in five-year survival for mismatched-related donor transplantation (62% ± 4%) or umbilical cord blood transplantation (57% ± 6%) (p=0.68). Antoine et al (2003; n=919) also reported three-year survival for SCID by donor type which was significantly better for HLA identical transplant (77%) than HLA-mismatched transplant (54%) (p=0.002).

For WAS patients overall survival was 82% (Moratto et al 2011; n=194) and five-year survival was 70% (95%CI 63 to 77) in Filipovitch et al (2001; n=170) and 83% and 90% respectively for patients treated before and after the year 2000 ($p<0.05$) (Moratto et al (2011; n=194). Moratto et al (2011) also reported eight-year survival as 75% after 2000 and 73% before 1999 ($p<0.05$). One study (n=249) reported five-year survival for haemophagocytic lymphohistiocytosis (HLH) patients as 66% ± 8% (Trottestam et al 2011). For patients with X-linked hyper IgM syndrome overall survival was 85% for patients receiving HSCT (n=67) and 80% for patients without HSCT (n=109) (with no significant difference between the groups, p=0.671) (de la Morena et al 2017).

One study (n=606) reported long term survival for patients who had survived more than two years after HSCT (Eapen et al 2012). For this sub-group of patients, nine-year survival was 92% for SCID patients and 96% for non-SCID patients. Seven-year survival was also reported with similar results.

Ten studies performed multivariate analysis to identify risk factors affecting survival. The comparisons made varied, but recurring risk factors across studies that significantly affected survival included age at HSCT (favouring younger ages), donor type (favouring matched sibling donors) and infection prior to HSCT (favouring no infection).

Mortality

Mortality outcomes were reported by three uncontrolled studies. Mitchell et al (2013; n=135) reported the cumulative incidence of transplant-related mortality at 100 days in patients with any PID as 10% (confidence intervals not reported). Hassan et al (2012; n=106) reported mortality in the first 100 days after HSCT in ADA-SCID[9] patients as 20% (confidence intervals not reported). Mitchell et al (2013) also reported the cumulative one-year incidence of transplant-related mortality in PID patients as 22% (confidence intervals not reported). In multivariate analysis, increased risk of transplant-related mortality was significantly associated with active cytomegalovirus disease, interstitial pneumonitis and veno-occlusive disease ($p<0.05$) (Mitchell et al 2013). Eapen et al (2012; n=606) reported relative mortality rate for PID patients compared to the general population. The excess deaths per 1,000 compared to an age, sex and nationality matched population was 54 (95%CI 28 to 79) for SCID and 38 (95%CI 25 to 51) for non-SCID for two to six years after HSCT. In six to ten years after HSCT there was no significant difference in mortality risks for surviving patients compared to the general population (p value not reported).

Engraftment

Engraftment was reported in eight uncontrolled studies covering the proportion of patients achieving engraftment, neutrophil counts and platelet counts.

Pai et al (2014; n=240) reported that 72% of SCID patients achieved engraftment after a single HSCT. Hassan et al (2012) reported an engraftment rate of 90% for 40 unconditioned ADA-SCID patients. Filipovitch et al (2001) reported that 89% of 87 WAS patients had donor cell engraftment after the first HSCT. de la Morena et al (2017; n=176) included patients with X-linked hyper IgM syndrome and reported engraftment rates of 93% for myeloablated[10] patients and 85% for non-myeloablated patients (with no significant difference between the groups, p=0.384). Antoine et al (2003) reported the proportion of SCID (n=475) and non-SCID (n=444) patients achieving sustained engraftment by donor type. Sustained engraftment rate was significantly better for SCID patients receiving an HLA-identical transplant (96%) than an HLA-mismatched transplant (90%) (OR 2.7 95%CI 1.2 to 7.4). The proportion of non-SCID patients achieving sustained engraftment was 99% for genotypically HLA-matched, 81% for phenotypically HLA-matched, 75% for HLA-mismatched from a related donor and 79% for an unrelated donor transplant.

Mitchell et al (2013; n=135) reported neutrophil engraftment[11] in PID patients as 89% with a median time to engraftment of 16 days (range 1-62). Fernandes et al (2012) reported rates of neutrophil engraftment[12] in SCID patients as 78% for 162 patients receiving a mismatched-related donor transplantation and 86% for 70 patients receiving an umbilical cord blood transplantation.

[9] Adenosine deaminase (ADA) SCID accounts for 10-20% of all SCID (Hassan et al 2012)

[10] Myeloablation is suppression of bone marrow to produce blood cells e.g. by chemotherapy or radiation therapy prior to bone marrow transplantation

[11] The first of three consecutive days of absolute neutrophil count of $\geq 0.5 \times 10^9$/L

[12] Absolute neutrophil count of $\geq 0.5 \times 10^9$/L for 3 consecutive days and/or donor chimerism

Mitchell et al (2013; n=135) reported platelet engraftment in PID patients as 85% with a median time to engraftment of 30 days (range 1-112), where platelet engraftment was defined as a platelet count of ≥20x10^9/L measured a minimum of seven days after last platelet transfusion. Moratto et al (2011; n=194) reported that 24% of patients with WAS did not achieve normalisation of the platelet count (i.e. <150x10^9/L), implying that 76% did achieve normalisation.

Chimerism

Chimerism (the presence of donor cells after transplant) was reported by three uncontrolled studies. In Moratto et al (2011; n=194), 28% of WAS patients showed mixed chimerism in at least one of the cell lineages tested (T lymphocytes, B lymphocytes, myeloid cells) 12 months or more after HSCT). Low or null donor chimerism[13] was more common within myeloid cells (16.5%) than in B lymphocytes (7.4%) or T lymphocytes (3.2%). In Pai et al (2014; n=240), significantly fewer SCID patients from mismatched related donors had full or mixed donor B-cell chimerism (39%) compared to matched sibling donors (80%) and other donors (71%) (p<0.001). Fernandes et al (2012) reported that for patients who survived more than six months after HSCT, significantly more SCID patients receiving an umbilical cord blood transplantation (n=36) achieved full donor chimerism (75%) compared to 77 SCID patients receiving a mismatched-related donor transplantation (33%) (p=0.001).

Immunologic reconstitution

Immunologic reconstitution outcomes were reported in eight uncontrolled studies covering T and B cell counts and requirement for intravenous immunoglobulin (IVIG).

Moratto et al (2011; n=194) reported immunologic reconstitution ≥12 months after HSCT. 68% of WAS patients showed normalisation of the absolute count of T and B lymphocytes and of T lymphocyte subsets. Filipovitch et al (2001) reported that 91% of 154 WAS patients who survived 28 or more days after HSCT achieved haematopoietic recovery after first HSCT. The remaining five studies all included SCID patients. Pai et al (2014; n=240) reported that 70% of patients had $CD3^+$ T-cell counts of >1,000/mm^3 after two years, and found that donor type (favouring matched sibling donors), conditioning regimen (favouring reduced–intensity or myeloablative) and lymphocyte phenotype (favouring B^+) were significantly associated with achieving this T-cell count level in multivariate analysis (p<0.05). Schuetz et al (2014; n=145) reported that 61% had normalisation of $CD4^+$ T-cell numbers after two years and found that significant predictors of a normal T cell count were use of myeloablative conditioning and presence of donor myeloid chimerism[14] in multivariate analysis (p<0.002). Heimall et al (2017; n=100) reported that conditioned patients had higher $CD4^+$ counts than unconditioned patients but did not provide figures. Hassan et al (2012) reported outcomes for 55 patients with T cell data available at two years after HSCT by donor type. The proportion of patients with $CD3^+$ T-cell numbers >1,000/mm^3 were 79% for matched sibling donors, 60% for matched family donors, 71% for matched unrelated donor and 63% for haploidentical donor. The proportion of patients with $CD4^+$ T-cell numbers >300/mm^3 were 79% for matched sibling donors, 100% for matched family donors, 85% for matched unrelated donor and 100% for haploidentical donor. Fernandes et al (2012; n=249) reported that at six months, patients receiving an umbilical cord blood transplantation had a greater mean total lymphocyte count recovery (3,448[15]) compared to patients receiving a mismatched-related donor transplantation (2,227) (p=0.01). This comparison was also significant at 12 months (5,207 vs. 3,690; p=0.008), but there was no significant difference by 24 months. Fernandes et al did not find any significant differences between these two donor groups for $CD3^+$ or $CD4^+$ cell counts.

[13] Low chimerism was defined as 5% to 50% of donor cells. Null chimerism was defined as <5% donor cells (Moratto et al 2011)

[14] The presence of donor myeloid cells (e.g. monocytes and neutrophils) after transplantation

[15] No metric reported, but others report total lymphocyte count as mm^3

In Moratto et al (2011; n=194), 87% of WAS patients did not require IVIG at follow-up. Three studies included SCID patients and reported the proportion of patients that did not require IVIG[16] as 53% (Schuetz et al 2014; n=145), 89% (Hassan et al 2012; n=106) and 42% (Railey et al 2009; n=161). Heimall et al (2017; n=100) reported that significantly more SCID patients who received conditioning prior to HSCT did not require IVIG (47%) compared to unconditioned SCID patients (14%) (p=0.003). In Fernandes et al (2012; n=249) significantly more SCID patients receiving an umbilical cord blood transplantation discontinued IVIG (45% ± 6%) compared to SCID patients receiving a mismatched-related donor transplantation (31% ± 4%) (p=0.02). In Schuetz et al's (2014) multivariate analysis, long-term requirement for IVIG was associated with the ARTEMIS gene defect deficiency, poor T-cell reconstitution, requirement of an additional transplant procedure and HSCT from a haploidentical donor (p<0.05) in SCID patients. In Pai et al's (2014; n=240) multivariate analysis, independence from IVIG therapy at two years was significantly associated with donor type (favouring matched siblings) and conditioning regimen (favouring reduced-intensity or myeloablative conditioning) (p<0.05) in SCID patients.

Requirement for more than one HSCT

Requirement for more than one HSCT was reported by eight uncontrolled studies. In two studies including patients with any PID this was 11% (Cole et al 2012; n=111) and 13% (Mitchell et al 2013; n=135). In three studies of SCID patients an additional HSCT was required in 9% (Heimall et al 2017; n=100), 18% (Pai et al 2014; n=240) and 25% (Railey et al 2009; n=161) of patients. In Fernandes et al (2012; n=249) significantly more SCID patients receiving a mismatched-related donor transplantation required a second HSCT (28%) compared to SCID patients receiving an umbilical cord blood transplantation (9.5%) (p=0.002). In the remaining two studies more than one HSCT was required by 13% of patients with X-linked hyper IgM syndrome (de la Morena et al 2017; n=176) and 14% of WAS patients (Filipovitch et al 2001; n=170).

Admission to intensive care

Rates of admission to intensive care were reported by one uncontrolled study of patients with any PID (Cole et al 2012; n=111). 35% of patients required at least one ICU admission at a median of 31 days after HSCT for the first admission (range -6 to 834). The most common reason for admission was respiratory problems[17] (59%). Other reasons included surgical problems (17%), complications related to veno-occlusive disease (9%), cardiovascular instability (5%), infection (5%) and neurological problems (5%). The median duration of admission was 6 days (range 1-35).

Post-transplant malignancy

Post-transplant malignancy was reported by one uncontrolled study of patients with any PID (Kamani et al 2011; n=2,266). 52 patients (2.3%) developed a confirmed post-transplant malignancy, of whom 40 had died at follow-up. The cumulative incidence of malignancy was 2% (95%CI 2 to 3) at five and ten years and 3% (95%CI 2 to 5) at 15 years. The cumulative incidence was higher in WAS patients (4%, 95%CI 2 to 6 at five, ten and 15 years) than SCID patients (2%; 95%CI 1 to 3 at five and ten years and 3%; 95%CI 1 to 6 at 15 years). Lymphoproliferative disorders were the most common malignancy occurring in 45 patients (87% of malignancies) with a median time to development of three months after HSCT (range 1-41). Kamani et al report that the overall risk of cancer in children with PID is 4%.

[16] Some studies reported a figure for patients that did require IVIG. This is translated into the figure that did not require IVIG here in order to summarise study findings

[17] The respiratory category included respiratory failure as a result of pneumonitis, pneumothorax, pulmonary haemorrhage, pulmonary hypertension, pleural effusion, respiratory arrest, pulmonary oedema and undefined causes of respiratory deterioration

Activities of daily living
Activities of daily living, assessed using Karnofsky/ Lanksky scores, were reported in two uncontrolled studies (de la Morena et al 2017; Filipovitch et al 2001). de la Morena et al (2017) reported that 57 surviving patients with X-linked hyper IgM syndrome treated with HSCT had significantly higher median scores (100%) than 87 surviving patients who did not receive HSCT (90%) at last follow-up ($p<0.001$). Filipovitch et al (2001) included patients with WAS and reported that for 84% of 61 patients with data available, the score did not fall below 100% between two and 14 years after HSCT. A further 13% had a lowest score of 90%.

Quality of life
Outcomes relating to quality of life were reported by one uncontrolled study. Railey et al (2009) included SCID patients and assessed the quality of life of 111 surviving patients using a non-validated SCID-specific questionnaire developed by the study authors and sent to families. 86% of patients were considered to be healthy by their families, with 36% reporting no health problems in the last two years. Where health problems were reported the most common (affecting ≥10%) were persistent rash (25%), sinusitis (20%), asthma (14%), diarrhoea (14%), ADHD (21%) and developmental delay (10%). 12% of patients were below the 3rd percentile for height and weight and 3% required special schooling.

Centre assessment
Centre assessment of post-HSCT outcome for surviving patients was reported by one uncontrolled study of WAS patients (Filipovitch et al 2001). This reported that for 120 surviving patients, 53% were considered 'cured', 18% were considered 'improved', 3% were considered 'unchanged' and 3% were considered 'worse'. For 23% of patients the status was unknown. No definitions were provided for the categories used.

Safety

2. What is the evidence on safety of allogeneic HSCT in patients of all ages with primary immunodeficiencies, compared with any alternative treatment strategies?
No studies were identified comparing the safety of allogeneic HSCT with any alternative treatment strategies. In the absence of comparative data it is not always clear whether the complications reported are related to HSCT or to the PID.

Fourteen uncontrolled studies with median follow-up ranging from 25 months to 11 years reported safety outcomes including cause of death and adverse events. Trottestam et al (2011) reported that 67% of 42 deaths were transplant related. The most common cause of death following HSCT was infection accounting for between 20% and 76% of deaths reported by studies. Other often reported causes of death included GVHD, respiratory distress and organ failure. The most common causes of death in patients with X-linked hyper IgM syndrome who did not receive HSCT (reported in one study; n=176) were malignancy and liver failure (both 27%) and infection (23%) (de la Morena et al 2017).

Three studies reported adverse events following HSCT. Mitchell et al (2013; n=135) reported 70 adverse events after HSCT with the most common being cytomegalovirus disease (19%), interstitial pneumonitis (15%) and veno-occlusive disease (13%) (median follow-up six years). Moratto et al (2011; n=194) reported that 46% of patients experienced complications in the year after HSCT, with the most common being infection requiring hospitalisation (28%), autoimmune manifestations (14%) and GVHD (11%). In multivariate analysis, the only significant risk factor for complications was HSCT from a mismatched family donor compared to a matched sibling donor ($p<0.019$). Schuetz et al (2014) reported late clinical complications in 49% of 92 patients who had

survived more than two years after HSCT with the most common being autoimmune manifestations (24%), severe or recurrent infections (24%), poor growth (29%) and requirement for nutritional support (13%). In multivariate analysis the factors significantly associated with late clinical complications included diagnosis of the ARTEMIS gene defect, viral infection prior to HSCT, treatment with alkylator agents, requirement of an additional HSCT procedure and requirement for IVIG ($p<0.01$).

Six studies reported the proportion of patients experiencing GVHD. In de la Morena et al (2017) 40% of 67 HSCT patients experienced GVHD. The proportion of patients experiencing acute GVHD (grade II to IV) at 100 days was 19% (95%CI 12 to 28) (Heimall et al 2017; n=100), 20% (95%CI 17 to 28) (Pai et al 2014; n=240) and 25% (confidence intervals not reported) (Mitchell et al 2013; n=135). In Fillipovitch et al (2001) this was 36% in 160 patients surviving at least 21 days after HSCT. The proportion of patients experiencing acute GVHD (grade III to IV) at 100 days was 8% (95%CI 4 to 15) (Heimall et al 2017) and 8% (95%CI 5 to 12) (Pai et al 2014). In Fernandes et al (2012; n=249) there was no significant difference in acute grade II-IV GVHD for mismatched-related donor transplantation (22% ± 3%) or umbilical cord blood transplantation (34% ± 6%) ($p=0.06$). The proportion of patients experiencing chronic GVHD at two years was 16% (95%CI 9 to 24) (Heimall et al 2017) and 15% (95%CI 10 to 20) (Pai et al 2014) and was 16% at one year (confidence intervals not reported) (Mitchell et al 2013). In Fillipovitch et al (2001), 23% of 141 patients surviving at least 90 days after HSCT developed chronic GVHD. In Fernandes et al (2012) significantly more patients receiving an umbilical cord blood transplantation experienced chronic GVHD (22%) compared to mismatched-related donor transplantation (10%) ($p=0.03$). In multivariate analysis, decreased risk of GVHD was associated with use of a fully matched sibling donor and HSCT performed after 1998 ($p=0.002$) (Mitchell et al 2013).

Cost effectiveness

3. What is the evidence for the cost-effectiveness of allogeneic HSCT in patients of all ages with primary immunodeficiencies, compared with any alternative treatment strategies?
No studies assessing the cost-effectiveness of allogeneic HSCT in patients with PID were identified.

Patient selection

4. Is it possible to identify particular sub-groups of patients who would derive a net clinical benefit from allogeneic-HSCT?
No studies directly addressed the question of whether any sub-groups of patients would derive a greater net clinical benefit from allogeneic HSCT.

Studies included patients with a range of PID conditions. However differences in the patient populations and reporting of outcomes make it difficult to compare results between studies.

A number of studies reported the impact of different risk factors on outcomes in multivariate analysis. These results were discussed with the relevant outcomes above and in the tables in section 7.

5 Discussion

Sixteen uncontrolled studies were included with between 100 and 2,266 PID patients. Six of these included patients with any PID and ten focused on one type of PID. Five of the 16 studies included patients who were more than 18 years old at HSCT.

Descriptive results from uncontrolled studies provide evidence of generally positive outcomes after HSCT for surviving PID patients on a range of outcome measures, with most studies reporting survival rates of over 70%. Where statistical analysis was performed, this tended to explore outcomes for sub-groups of PID patients receiving HSCT. The comparisons performed varied but common features that recurred in different studies included better outcomes for patients who received HSCT in more recent years; who had a genotypically matched donor, who received HSCT at a younger age or who did not have an infection prior to HSCT.

The studies did not provide evidence for the effectiveness of HSCT compared to alternative treatment strategies.

Although several studies included patients with a wide age range, the highest reported median age at HSCT was 40.7 months (i.e. 3.3 years). The median follow-up after HSCT varied from 25 months to 11 years. Where reported, approximately half of surviving patients still experienced complications one and two years after HSCT. Longer follow-up of these patients will provide better evidence of any longer term impacts.

Many of the studies combined data from multiple worldwide centres over a long period of time. These have the advantage of drawing on a large number of patients, but introduce potential sources of bias around differences in practices between centres or changes in practice over time. When year of HSCT was assessed within study analysis, patients receiving HSCT more recently often had significantly better outcomes.

It is possible that the same patients may have been included in more than one of the studies. Half of the included studies used data from centres worldwide, although they often focused on a specific sub-group of PID patients which may reduce the risk of duplication.

6 Conclusion

The evidence identified for allogeneic HSCT for PID included 16 uncontrolled studies with 100 or more PID patients.

The uncontrolled studies describe generally positive outcomes after HSCT for surviving PID patients on a range of outcome measures. The studies did not provide evidence considering the effectiveness of HSCT compared to alternative treatment strategies.

Overall, the evidence base is limited to uncontrolled studies, most of which were 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**
Heimall et al (2017)	P1 – prospective study Patients treated at 25 centres in the US between 2010 and 2014	Patients with SCID Median age at HSCT 103 days (range 16 to 1,630)	n=100 HSCT Median follow-up 25 months (range 10 to 51)	Clinical effectiveness	Survival	2-year survival 90% (95%CI 80-95) No multivariate analysis reported. Authors stated that multivariate analysis of risk factors was limited by sample size	6	Direct	This uncontrolled prospective study included patients treated in 25 centres over a 4 year period and had a moderate sample size. The prospective design of the study reduces the possibility of selection bias in the study population. However variation between the different centres remains a source of potential bias. As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments.
				Clinical effectiveness	Immuno-logic reconstitution	Conditioned patients had higher $CD4^+$ counts and were significantly more likely not to require IVIG (47%) than unconditioned patients (14%) (p=0.003)			
				Clinical effectiveness	Requirement for more than one HSCT	9 patients (9%) required a 2nd HSCT			
				Safety	Safety	Cause of death (n=11): • Infection 45% • Sinusoidal obstruction syndrome[18] 18% • GVHD 18% • Respiratory failure 9% • Encephalopathy 9% GVHD[19] • Acute GVHD grade II-IV at 100 days: 19% (95%CI 12 to 28) • Acute GVHD grade III-IV at 100 days: 8% (95%CI 4 to 15) • Chronic GVHD at 2 years 16%			

[18] Also known as veno-occlusive disease

[19] In graft versus host disease (GVHD) the donated cells react against the patient's body which can lead to an immune response attack. GVHD is graded as I – mild; II – moderate; III – severe; IV – life threatening

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Study reference	**Study design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of evidence score**	**Applicability**	**Critical appraisal summary**
						(95%CI 9 to 24)			
de la Morena et al (2017)	S2 – Retrospective multinational review of patient records Data provided by physicians from 28 clinical sites worldwide for patients diagnosed between 1964 and 2013	Patients with X-linked hyper IgM syndrome Median age at HSCT 2.9 years (range 0.1 to 24)	n=176 67 (38%) received HSCT Mean follow-up 8.5 ± 7.2 years (range 0.1 to 36.2 years)	Clinical effectiveness	Survival	Overall survival 85% for patients receiving HSCT and 80% for patients without HSCT (no significant difference between groups, p=0.671) Age at HSCT predicted survival. Survival was higher for patients receiving HSCT < 5 years old compared to > 5 years old (p=0.03) and for patients receiving HSCT < 10 years old compared to > 10 years old (p=0.01) In multivariate analysis liver disease at time of diagnosis was a negative predictor of overall survival (p<0.001)	6	Direct	This uncontrolled study retrospectively compared outcomes for two cohorts of patients treated at 28 sites over a 49 year period. However, it is not a comparative study. Reasons why patients did not receive HSCT are not reported. Factors included in multivariate analysis included respiratory tract involvement, hematologic involvement, gastrointestinal disease, liver/biliary involvement, CNS involvement, failure to thrive, malignancy and history of infection For HSCT recipients, risk factors considered included age at HSCT, year of HSCT, donor type, stem cell source, conditioning regimen, engraftment and GVHD. The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the 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 comparable patients receiving alternative treatments.
				Clinical effectiveness	Activity of daily living	Activity of daily living at last follow-up assessed by Karnofsky/ Lansky age performance scores[20] 57 surviving patients treated with HSCT had higher median Karnofsky/ Lansky age performance scores (100%) compared to 87 surviving patients without HSCT (90%) (p<0.001)			
				Clinical effectiveness	Engraftment [21]	Engraftment rates presented for myeloablated[22] (93%) and non-			

[20] Karnofsky/ Lansky scores are used to determine functional status. The Karnofsky Scale is designed for people aged ≥16 years and the Lansky Scale is designed for people <16 years old. Both scales are scored from 10 to 100. Higher scores indicate better function (CIBMTR 2009). 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.

[21] 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

[22] Myeloablation is suppression of bone marrow to produce blood cells e.g. by chemotherapy or radiation therapy prior to bone marrow 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**
						myeloablated (85%) patients (no significant difference between groups (p=0.384)			
				Clinical effectiveness	Requirement for more than one HSCT	9 (13%) patients had >1 HSCT			
				Safety	Safety	Cause of death with HSCT (n=10) • Infection 40% • GVHD 20% • Liver failure 20% • Veno-occlusive disease 10% • Progressive disease neurologic deterioration of unknown cause 10% Cause of death without HSCT (n=22) • Malignancy 27% • Liver failure 27% • Infection 23% • Central nervous system 9% • Unknown cause 14% 27 patients (40%) had GVHD, of which 20 were acute			
Pai et al (2014)	S2 – Retrospective review of patients treated at 25 centres between 2000 and 2009 (geography not specified)	SCID patients Median age at HSCT 180 days (i.e. 6 months) (8-1,162 days)	n=240 HSCT Median follow-up not reported	Clinical effectiveness	Survival	5-year survival 74% (95%CI 68 to 79) Multivariate analysis: • Age at HSCT and infection status were significantly associated with survival (p<0.05) (favouring age <3.5 months if an active or resolved infection was present (i.e. no significant difference by age if no infection was present) • Survival was also significantly associated with donor type (p<0.05) (favouring matched sibling donor)	6	Direct	This uncontrolled retrospective review included patients from 25 centres over a 9 year period and had a moderate sample size. Risk factors included in multivariate analysis included age at HSCT, sex, race or ethnic group, maternal engraftment, genotype, phenotype, family history, infection status, failure to thrive, donor type, use of conditioning, graft type, type of T-cell depletion and GVHD prophylaxis. The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of

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**
				Clinical effectiveness	Engraftment	72% engraftment after a single HSCT			patient details to the database, the patients included in the analysis and the 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.
				Clinical effectiveness	Immuno-logic reconstitution	**T-cell count** 70% had $CD3^+$ T-cell counts >1,000/mm^3 after 2 years In multivariate analysis, donor type (favouring matched sibling), conditioning regimen (favouring reduced-intensity or myeloablative conditioning) and lymphocyte phenotype (favouring B^+) were significantly associated with achieving $CD3^+$ T-cell counts >1000/mm^3 ($p<0.05$). **Independence from IVIG therapy after 2 years** In multivariate analysis, donor type (favouring matched sibling donors), and conditioning regimen (favouring reduced-intensity or myeloablative conditioning) were significantly associated with independence from IVIG ($p<0.05$)			
				Clinical effectiveness	Chimerism[23]	Significantly fewer patients from mismatched[24] related donors (39%) had full or mixed donor B-cell chimerism compared to matched sibling donors (80%) and other donors (71%) ($p<0.001$)			
				Clinical effectiveness	Requirement for more than one	Boost or 2nd transplant at 5 years: 18% (95%CI 13 to 23)			

[23] Chimerism is the presence of donor cells after transplantation. Mixed chimerism is a combination of patient and donor cells. In full chimerism only donor cells are present

[24] Mismatched donors are used when a matched donor is not available and do not have human leukocyte antigens that are identical to the 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**
					HSCT	Donor type, genotype and use or type of conditioning regimen were not significantly associated with graft failure			
				Safety	Safety	Cause of death (n=62): • Infections 39% • Pulmonary complications 37% • Acute GVHD 5% • Chronic GVHD 2% • Graft rejection or failure 2% • Other organ toxicity 13% • Unknown 3% GVHD • Acute GVHD grade II-IV at 100 days: 20% (95%CI 17 to 28) • Acute GVHD grade III-IV at 100 days: 8% (95%CI 5 to 12) • Chronic GVHD at 2 years 15% (95%CI 10 to 20)			
Schuetz et al (2014)	S2 – Retrospective review of medical records from patients treated at 3 centres in France, Germany and the US between 1985 and 2009	SCID patients with confirmed ARTEMIS and RAG deficiencies Median age at HSCT 7 months (0.5-56 months)	n=145 HSCT Median follow-up: ARTEMIS (n=69) 4.25 years (0.5 months-27.75 years) RAG (n=76) 2.67 years (1 month -27.75 years)	Clinical effectiveness	Survival	Overall survival 62% (95%CI 52 to 70) In multivariate analysis factors significantly associated with increased mortality were presence of viral infection prior to HSCT; age at diagnosis ≥3 months; chronic GVHD and need for retransplantation (p<0.01)	6	Direct	This uncontrolled retrospective review included patients from 3 centres over a 24 year period and had a moderate sample size. A sub-group of SCID is characterised by a lack of T and B cells caused by gene defects, including the ARTEMIS defect and the recombination activating gene (RAG1 and RAG2) deficiencies. Risk factors included in multivariate analysis included molecular diagnosis, viral infection prior to transplant, age at diagnosis, myeloablative conditioning, donor type, retransplantation, HSCT boost, early infection and chronic GVHD. The retrospective design of the study introduces
				Clinical effectiveness	Immuno-logic reconstitution	**T-cell count** Normalisation of $CD4^+$ T-cell numbers at 2 years after HSCT: 61% In multivariate analysis predictive factors of a normal T cell count were use of myeloablative conditioning and			

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**
						presence of donor myeloid chimerism[25] (p<0.002) **Independence from IVIG therapy** 47% required IVIG at last follow-up In multivariate analysis long-term requirement for IVIG was associated with ARTEMIS deficiency, poor T-cell reconstitution, requirement of an additional transplant procedure and HSCT from a haploidentical donor[26] (p<0.05)			the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the classification of details from patient records. As the study does not include a comparator treatment it is not possible to compare the outcomes for these patients with patients receiving alternative treatments.
				Safety	Safety	**For 92 patients who survived ≥2 years after HSCT:** 49% had 115 clinical events: • Autoimmune manifestations 24% • Severe or recurrent infections 24% • Poor growth 29% • Requirement for nutritional support 13% Additional non-infectious and non-autoimmune complications occurred exclusively in 7 of 47 patients with ARTEMIS deficiency In multivariate analysis, factors associated with late (≥2 years) clinical complications included ARTEMIS diagnosis, viral infection prior to HSCT, treatment with alkylator agents, requirement of an additional transplant procedure and IVIG requirement (p<0.01)			

[25] The presence of donor myeloid cells (e.g. monocytes and neutrophils) after transplantation
[26] A haploidentical donor is usually a 50% match to the patient e.g. a parent, sibling or child

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**
Mitchell et al (2013)	S2 – Retrospective review of patients treated at 6 centres in Australia and New Zealand between 1992 and 2008	Patients with PID Median age at HSCT 1 year (range 0-15 years) Most common PIDs were SCID (48%), WAS (20%) and CGD (12%)	n=135 HSCT Median follow-up 6.03 years (range 0.39-17.31 years)	Clinical effectiveness	Survival	5 year survival: 72% (confidence intervals not reported) On multivariate analysis decreased survival was significantly associated with active cytomegalovirus disease, interstitial pneumonitis and veno-occlusive disease ($p<0.05$) 5-year survival for the most common PIDS: • SCID 70% • WAS 81% • CGD 69%	7	Direct	This uncontrolled retrospective review included patients from 6 centres over a 17 year period and had a moderate sample size. Descriptive results by type of PID (with no analysis comparing outcomes by type of PID) are not reported here. Risk factors included in multivariate analysis included sex, age, year of HSCT, time from diagnosis to HSCT, donor-recipient relationship, donor-recipient HLA compatibility, stem cell source, donor and recipient cytomegalovirus seropositivity, pre-transplantation conditioning, GVHD and cytomegalovirus prophylaxis and incidence of adverse events immediately post-transplantation. The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the 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.
				Clinical effectiveness	Engraftment	**Overall neutrophil engraftment** (first of 3 consecutive days of absolute neutrophil count $\geq 0.5 \times 10^9$/L): 89% Median time to neutrophil engraftment: 16 days (range 1-62 days) **Overall platelet engraftment** (platelet count $\geq 20 \times 10^9$/L a minimum of 7 days after last platelet transfusion): 85% Median time to platelet engraftment: 30 days (range 1-112 days)			
				Clinical effectiveness	Transplantation related mortality	Cumulative incidence at 100 days: 10% Cumulative incidence at 1 year: 22% Confidence intervals not reported On multivariate analysis increased risk of transplantation related mortality was significantly associated with active cytomegalovirus disease, interstitial pneumonitis and veno-occlusive disease ($p<0.05$)			

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**
				Clinical effectiveness	Requirement for more than one HSCT	18 patients (13%) required a 2nd HSCT due to graft failure or rejection			
				Safety	Safety	Cause of death (n=36): • Infection 22% • Interstitial pneumonitis (non-infectious) 17% • GVHD 14% • Graft failure 14% • Organ failure 14% • Haemorrhage 11% • Acute respiratory distress syndrome (non-infectious) 8% Adverse events post-transplantation (n=70): • Cytomegalovirus disease 19% • Interstitial pneumonitis 15% • Veno-occlusive disease 13% • Haemorrhagic cystitis 4% 100 day cumulative incidence for acute GVHD (grade II to IV): 25% 1-year cumulative incidence for chronic GVHD: 16% On multivariate analysis decreased risk of GVHD was associated with use of a fully matched sibling donor and HSCT performed after 1998 (p=0.002)			
Eapen et al (2012)	S2 – Retrospective review of patient database 114 organisations	PID patients who survived > 2 years after HSCT and had normal T-cell function (SCID) or >95% donor chimerism	SCID n=201 Non-SCID n=405 HSCT Median follow-up of	Clinical effectiveness	Survival	For patients who survived >2 years after HSCT 7-year survival SCID: 93% (95%CI 89 to 97) Non-SCID: 96% (95%CI 94 to 98) 9-year survival	5	Direct	This uncontrolled retrospective review included patients from 114 centres worldwide over a 23 year period and had a moderate sample size. This study also presented data for patients receiving HSCT due to inborn errors of metabolism. Only results for patients with SCID and non-SCID PID are reproduced here.

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**
	worldwide who submitted data to the Center for International Blood and Marrow Transplant Research between 1980 and 2003 and had extended follow-up data on >85% of their surviving patients	(non-SCID) Median age at HSCT not reported Age at HSCT SCID: 79% <1 year and 97% <2 years Non-SCID: 27% <1 year, 63% <2 years and 3% >15 years	surviving patients SCID: 93 months (range 29-244) Non-SCID: 75 months (range 25-284)			SCID: 92% Non-SCID 96% (confidence intervals not reported)			Multivariate analysis was performed but not presented separately for the 2 patient groups (SCID and non-SCID) of interest in this review. The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the 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.
				Clinical effectiveness	Relative mortality rate	Excess deaths per 1,000 The risk of mortality was in excess of that to the age, sex and nationality matched general population 2-6 years after HSCT SCID: 54 (95%CI 28 to 79) Non-SCID: 38 (95%CI 25 to 51) 6-10 years after HSCT, mortality risks were not significantly different to that of the matched general population (p value not reported)			
				Safety	Safety	**Cause of death from 2-6 years after HSCT** SCID (n=10) • Infection without GVHD: 30% • Organ failure: 30% • Chronic GVHD: 20% • PTLD-EBV: 10% • Not reported : 10% Non-SCID (n=12) • Chronic GVHD:42% • Infection without GVHD: 17% • Acute myeloid leukaemia: 17% • PTLD-EBV: 8% • Graft failure: 8% • Accidental death: 8% **Cause of death >6 years after HSCT** SCID (n=4) • Infection without GVHD: 50% • Organ failure: 25% • Not reported : 25% Non-SCID (n=3)			

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**
						• Infection without GVHD: 33% • Brain stem glioma: 33% • Not reported : 33%			
Fernandes et al (2012)	S2 – Retrospective review of data from two European registries (Eurocord and SCETIDE) Data provided by 32 centres for patients treated between 1995 and 2005	Patients with SCID receiving a mismatched-related donor transplantation (MMRDT) or an umbilical cord blood transplantation (UCBT) Median age at HSCT MMRDT 6.5 months (range 1 to 35) UCBT 6.4 months (range 1 to 41)	n=249 (MMRDT 175, UCBT 74) HSCT Median follow-up MMRDT 58 months (range 3 to 157) UCBT 83 months (range 5 to 162)	Clinical effectiveness	Survival	**5-year survival** MMRDT: 62% ± 4% UCBT: 57% ± 6% No significant difference between MMRDT and UCBT (p=0.68) In multivariate analysis decreased survival was significantly associated with Omenn syndrome[27] vs SCID, failure to thrive pre-HSCT, diarrhoea pre-HSCT, viral infection pre-HSCT, reduced-intensity conditioning vs no conditioning, myeloablative conditioning vs no conditioning and use of anti-thymyocyte globulin or other mAb (p<0.05)	6	Direct	This uncontrolled retrospective review included patients from 32 centres taken from 2 European databases over a 10 year period and had a moderate sample size. The main focus of the study was to compare donor sources, but few centres used both donor sources so variation between centres is a potential source of bias. Risk factors included in multivariate analysis included donor type, year of HSCT, phenotype, failure to thrive, diarrhoea, Pretransplantation viral infection, conditioning regimen, use of anti-thymyocyte globulin or other mAb. The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the 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.
				Clinical effectiveness	Engraftment	In patients who survived >28 days after HSCT (n=162 MMRDT and n=70 UBCT) Engraftment (defined as absolute neutrophil count >0.5x10^9/L for 3 consecutive days and/or donor chimerism) MMRDT: 126 (78%) UCBT: 60 (86%) No significant difference between MMRDT and UCBT (p=0.14)			

[27] Omenn syndrome is an autosomal recessive form of SCID

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**
				Clinical effectiveness	Immuno-logic reconstitution	Lymphocyte count[28]: UCBT had greater total lymphocyte count recovery than MMRDT at 6 months (mean 3,448 vs 2,227, p=0.01) and 12 months (mean 5,207 vs 3,690, p=0.008) after HSCT. There was no significant difference at 24 months There was no significant difference in $CD3^+$ or $CD4^+$ cell counts between MMRDT and UCBT Independence from IVIG therapy: Significantly higher discontinuation of IVIG for UBCT (45% ± 6%) compared to MMRDT (31% ± 4%) (p=0.02)			
				Clinical effectiveness	Chimerism	For patients who survived >6 months after HSCT (n=77 MMRDT and n=36 UCBT): • No significant difference in full donor chimerism for $CD3^+$ T-cell compartment between MMRDT (88%) and UCBT (97%) (p=0.29) • Significantly more UCBT patients (75%) achieved full donor chimerism compared to MMRDT (33%) (p=0.001) Ranges/confidence intervals not reported			
				Clinical effectiveness	Requirement for more than one HSCT	Significantly more 2nd HSCTs for MMRDT (46; 28%) compared to UCBT (7; 9.5%) (p=0.002)			
				Safety	Safety	Cause of death (n=97; 67 MMRDT and 30 UCBT) MMRDT			

[28] No metric reported, but others report total lymphocyte count as mm^3

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**
						• Infection 46% • Acute respiratory distress syndrome 22% • GVHD 9% • Rejection 7% • Hepatic sinusoidal obstruction syndrome 3% • Multi-organ failure 1% • Secondary malignancy 3% • Other 7% UCBT • Infection 30% • GVHD 20% • Acute respiratory distress syndrome 20% • Rejection 7% • Cardiac toxicity 7% • Multi-organ failure 7% • Secondary malignancy 3% • Other 7% Acute grade II-IV GVHD MMRDT: 22% ± 3% UBCT: 34% ± 6% No significant difference between MMRDT and UCBT (p=0.06) Chronic GVHD MMRDT: 10% ± 2% UBCT: 22% ± 5% Significantly higher for UBCT than MMRDT (p=0.03)			
Hassan et al (2012)	S2 – Retrospective review of patients treated at 16 centres	Patients with ADA-SCID Median age at HSCT 4 months (range	n=106 HSCT Median follow-up 6.5	Clinical effectiveness	Survival	Overall survival: 67% (no confidence intervals reported) In multivariate analysis: • Survival was significantly associated with donor type	6	Direct	This uncontrolled retrospective review included patients from 16 worldwide centres over a 28 year period and had a moderate sample size, focusing on patients with one form of SCID. Adenosine deaminase (ADA)-SCID accounts for 10-20% of all SCID.

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**
	worldwide between 1981 and 2009	2 weeks to 7 years)	years (range 1.6 to 27.6)			(favouring matched donors) ($p<0.05$) • Survival was not significantly associated with conditioning, age at HSCT or stem cell source			Degree of chimerism was reported graphically by donor type but with no absolute figures that can be reproduced here The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the 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.
				Clinical effectiveness	Transplantation related mortality	Mortality from deaths in the 1st 100 days after HSCT: 20% (no confidence intervals reported)			
				Clinical effectiveness	Engraftment	Engraftment rate unconditioned patients (n=40): 90%			
				Clinical effectiveness	Immuno-logic reconstitution	For 55 patients with T cell data available $CD3^+$ T-cell numbers >1,000/mm^3 at 2 years after HSCT: • Matched sibling donor: 79% • Matched family donor: 60% • Matched unrelated donor: 71% • Haploidentical donor: 63% $CD4^+$ T-cell numbers >300/mm^3 at 2 years after HSCT: • Matched sibling donor: 79% • Matched family donor: 100% • Matched unrelated donor: 85% • Haploidentical donor: 100% **Independence from IVIG therapy** Of 46 patients with data available, 41 (89%) had discontinued IVIG			
				Safety	Safety	**Cause of death (n=35)** • Pneumonitis/respiratory failure and sepsis >50% (precise figure not reported) • GVHD 15% • Fungal infection 11% • Other (figure not specified)			
Cole et al (2012)	S2 – Retrospective	Patients with PID	n=111	Clinical effectiveness	Survival	Overall survival 76% (no confidence intervals reported)	6	Direct	This uncontrolled retrospective review included patients from a single UK centre over a 5 year

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**
	review of patients treated at one UK centre between 2005 and 2009	Median age at HSCT 1 year 4 months (range 1 month to 19 years 4 months) Most common PID was SCID (32%)	HSCT Follow-up period not reported	Clinical effectiveness	Admission to intensive care	39 (35%) had ≥1 admission to PICU/ adult ICU[29] at a median of 31 days after transplant for 1st admission (range -6 to 834 days) Reasons for admission: • Respiratory problems 59% • Surgical problems 17% • Complications related to veno-occlusive disease 9% • Cardiovascular instability 5% • Infection 5% • Neurological problems 5% Median duration of admission was 6 days (range 1-35 days) No significant association between age, sex, underlying diagnosis, donor type, source of stem cells, conditioning type and presence of infection at or immediately before HSCT and need for admission to intensive care			period and had a moderate sample size. In reasons for admission: • The respiratory category of included respiratory failure as a result of pneumonitis, pneumothorax, pulmonary haemorrhage, pulmonary hypertension, pleural effusion, respiratory arrest, pulmonary oedema and undefined causes of respiratory deterioration • The surgical problems category included elective post-operative admissions following laparotomy or splenectomy, elective femoral line insertion, perforated gastric ulcer and acute abdomen of unknown aetiology • Neurological problems included seizures or encephalopathy The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the 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.
				Clinical effectiveness	Requirement for more than one HSCT	12 patients (11%) required unconditioned boost transfusions			

[29] There was 1 adult ICU admission. The total number of adults in the sample is not reported

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**
Kamani et al (2011)	S2 – Retrospective multicentre review of patient database Organisations worldwide who submitted data to the Center for International Blood and Marrow Transplant Research between 1968 and 2003	Patients with PID Median age at HSCT 1 year (range 1.2 months to 47 years) Most common PIDs were SCID (47%) and WAS (16%)	n=2,266 HSCT Median follow-up 6 years (range 4 to 14)	Clinical effectiveness	Post-transplant malignancy	52 patients (2.3%) developed confirmed post-transplant malignancy Cumulative incidence of post-HSCT malignancy • 5-year: 2% (95%CI 2 to 3) • 10-year: 2% (95%CI 2 to 3) • 15-year: 3% (95%CI 2 to 5) • Unknown (10%) For SCID patients the cumulative incidence was 2% (95%CI 1 to 3) at 5 and 10 years and 3% (95%CI 1 to 6) at 15 years For WAS patients the cumulative incidence was 4% (95%CI 2 to 6) at 5, 10 and 15 years Lymphoproliferative disorders were the most common malignancy, occurring in 45 patients (87%) with a median time to development of 3 months after HSCT (range 1-41)	7	Direct	This uncontrolled retrospective review included patients from centres worldwide over a 35 year period and had a large sample size. The Center for International Blood and Marrow Transplant Research is a group of over 500 transplant centres worldwide that voluntarily contribute data on HSCT recipients. The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the classification of details from patient records. In this study, patients transplanted at inactive centres or centres that did not respond to a request to participate were excluded from the analysis (n=143 patients from 7 centres) to try to minimise reporting bias. Descriptive results by type of PID (with no analysis comparing outcomes by type of PID) are not reported here. As the study does not include a comparator it is not possible to compare the outcomes for these patients with patients receiving alternative treatments.
				Safety	Safety	Cause of death for 40 patients with malignancy who had died at follow-up: • Post-transplant malignancy (73%) • GVHD (7.5%) • Infection without GVHD (10%) 849 (38%) of patients with no malignancy had died at follow-up. No causes of death reported for these patients			
Trottestam et al (2011)	P1 – prospective study Patients recruited from	Patients with HLH, no previous cytotoxic or cyclosporine A therapy and no	n=249 124 (50%) received HSCT	Clinical effectiveness	Survival	**Patients who received HSCT** 5-year survival 66% ± 8% No significant difference in 5-year cumulative survival for patients with active disease at HSCT (n=43; 58%,	5	Direct	This uncontrolled prospective study included patients treated in 25 countries over a nine year period and had a relatively large sample size. The patients who did not have HSCT included those who died before HSCT could be performed

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**
	25 countries worldwide between 1994 and 2003	known underlying chronic or malignant disease Aged < 16 years Median age at therapy initiation 8 months (range 2 days to 15 years)	Median follow-up 6.2 years (range 0.4 to 13.7)			95%CI 43 to 73) compared to no active disease at HSCT (n=75; 72%, 95%CI 62 to 82) (p=0.06) No significant difference in survival for patients who received HSCT at <6 months after therapy initiation (60%), between 6 months and 1 year (68%) and >1 year (80%)			and patients who were assumed to have secondary HLH because they had no active disease for >1 year after non-HSCT therapy. Results for these patients are therefore not presented as primary immunodeficiencies are of interest in this review. The study does not compare outcomes for PID patients who did or did not receive HSCT. Quality of life outcomes were assessed using study-specific questionnaires completed at the time of HSCT, 100 days afterwards and then annually. The prospective design of the study reduces the possibility of selection bias in the study population.
				Safety	Safety	Cause of death (n=42 patients who received HSCT): • Transplant related (67%) • Graft failure and HLH reactivation (19%) • Multi-organ failure (7%) • Respiratory infection (2%) • Active HLH 2 days after HSCT (2%) • Complications of a surgical procedure (2%)			
Moratto et al (2011)	S2 – Retrospective multicentre review of patient data Patients treated at 12 European and American centres between 1980 and 2009 who entered data into a common electronic spreadsheet	Patients with WAS Median age at HSCT 34.6 months (range 2 months to 240 months (ie 20 years))	n=194 HSCT Median follow-up 76.8 months (6.4 years) (range 12 to 346 months)	Clinical effectiveness	Survival	Overall survival was 82% (no confidence intervals reported) **8-year survival** Significantly higher for patients who received HSCT after 2000 (74.9%) compared to before 1999 (73.4%) (p<0.05) **5-year survival** Significantly higher for patients who received HSCT after 2000 (89.9%) compared to before 1999 (83.3%) (p<0.005) In multivariate analysis better survival was associated with HSCT after 2000 (p<0.05). Reduced survival was associated with use of mismatched	7	Direct	This uncontrolled retrospective review included patients from 12 European and American centres over a 29 year period and had a moderate sample size. Risk factors included in multivariate analysis included year of HSCT, age at HSCT, clinical score, donor type, conditioning regimen, autoimmunity, acute GVHD (grade III or IV) and extensive chronic GVHD. The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the classification of details from patient records. As the study does not include a comparator it is

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**
						family donor or cord blood (p<0.05)			not possible to compare the outcomes for these patients with patients receiving alternative treatments.
				Clinical effectiveness	Engraftment	24% did not achieve normalisation of the platelet count (i.e. <150x10^9/L)			
				Clinical effectiveness	Immuno-logic reconstitution	At ≥12 months after HSCT: 68.3% patients showed normalisation of the absolute count of T and B lymphocytes and of T lymphocyte subsets 13% required IVIG			
				Clinical effectiveness	Chimerism	At ≥12 months after HSCT: 28% showed mixed chimerism in at least one of the cell lineages tested (T lymphocytes, B lymphocytes, myeloid cells). Low (5-50% donor cells) or null (<5% donor cells) donor chimerism: • myeloid cells 16.5% • B lymphocytes 7.4% • T lymphocytes 3.2%			
				Safety	Safety	Cause of death (n=35): • Infection without GVHD 46% • GVHD 20% • Malignancy or malignancy + infection 11% • Graft failure/rejection + infection 9% • Haemorrhage 6% • Other 9% 45.9% patients experienced complications in the year after HSCT. Complications included: • Infection requiring hospitalisation 28% • Autoimmune manifestations 14% • GVHD 11%			

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 graft failure or graft rejection 7% In multivariate analysis, the only statistically significant risk factor for complications was transplantation from a mismatched family donor compared to a matched sibling donor (p=0.019)			
Gennery et al (2010)	S2 – Retrospective multicentre review of patient registry Patients treated at 37 European centres between 1968 and 2005 recorded in the SCETIDE database	Patients with PID (SCID or non-SCID) Median age at HSCT is presented by donor type and year of HSCT and ranges from 4.2 to 13.1 months for SCID and 17.1 to 50.5 months for non-SCID (ranges not reported)	n= 1,482 (699 SCID 783 non-SCID) HSCT Median follow-up from HSCT is presented by donor type and year of HSCT and ranges from 1.0 to 9.6 years for SCID and1.2 to 9.5 years for non-SCID (range limits cover 0.0 to 32.6 years)	Clinical effectiveness	Survival	**SCID** 5-year survival by year of HSCT • 2000-2005: 71% (95%CI 63 to 80) • 1995-1999: 70% (95%CI 63 to 79) • <1995: 56% (95%CI 51 to 62) 5-year survival not reported for the whole population In multivariate analysis, increased survival was significantly associated with age <6 months at transplant (compared to >12 months), SCID B^+ phenotype (compared to B^-), recipient/donor compatibility (favouring a matched related donor), no pre-existing respiratory infection, no septicaemia, use of a protected environment, use of antibiotic prophylaxis and the absence of T-lymphocyte depletion (p<0.05) **Non-SCID** 4-year survival by year of HSCT • 2000-2005: 69% (95%CI 60 to 78) • 1995-1999: 58% (95%CI 51 to 65) • <1995: 54% (95%CI 49 to 61) 4-year survival not reported for the whole population In multivariate analysis, increased survival was significantly associated with recipient/donor compatibility	6	Direct	This uncontrolled retrospective review included patients from 37 European centres over a 37 year period and had a large sample size. Risk factors included in multivariate analysis included year of HSCT, age at transplant, SCID phenotype, recipient/donor compatibility, pre-existing respiratory infection, septicaemia, viral infection, protected environment, antibiotic prophylaxis and the presence or absence of T-lymphocyte depletion. The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the 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.

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**
						(favouring a matched related donor), no pre-existing respiratory impairment, no malnutrition and use of co-trimoxazole prophylaxis (p<0.05)			
Railey et al (2009)	S2-Retrospective review of patients treated at 1 US centre between 1982 and 2008	Patients with SCID who did not receive pre-transplant chemotherapy or post-transplant GVHD prophylaxis Median age at HSCT not reported	n=161 HSCT Median follow-up 8.7 years (range 2.9 to 14.1 years) Follow-up data for 111 survivors through surveys, 82 of which were also seen in clinic visits	Clinical effectiveness	Survival	Overall survival: 77% (no confidence intervals reported) 8-year survival was significantly higher for HSCT <3.5 months of age (96% 95%CI 84 to 99) compared to HSCT >3.5 months (70% 95%CI 60 to 77)	6	Direct	This uncontrolled retrospective review included patients from 1 US centre over a 16 year period and had a moderate sample size. Quality of life was assessed using a non-validated SCID-specific questionnaire developed by the study authors. The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the 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.
				Clinical effectiveness	Immuno-logic reconstitution	**For 111 patients surveyed:** 58% of patients receiving replacement IVIG 27% receiving standing antibiotics			
				Clinical effectiveness	Requirement for more than one HSCT	28 (25%) patients required ≥1 booster transplant			
				Clinical effectiveness	Quality of life	**For 111 patients surveyed:** 86% of patients were considered to be healthy by their families 36% reported no health problems in the last 2 years. Where health problems were reported these included: • Persistent rash 25% (3% chronic) • Sinusitis 20% • Asthma 14% • Diarrhoea 14% • Pneumonia 8% • Congenital hypothyroidism 6% • GERD 6% • Otitis media 5% • Oral aversion 5% • Intermittent haemolytic anaemia 2% • Liver transplant 2% • Cryptococcal osteomyelitis 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**
						Neurological problems: • ADHD 21% • Developmental delay 10% • Seizure disorder 2% • Cerebral palsy 2% Growth and development: • <3rd percentile height and weight 12% • Require special schooling 3%			
				Safety	Safety	**Cause of death (n=37):** • Viral infections 76% • Pulmonary disease 11% • Candida bloodstream infection 5% • Unrelated mitochondrial defect 3% • Nephrotic syndrome following chemotherapy prior to referral 3% • Veno-occlusive disease 3%			
Antoine et al (2003)	S2 – Retrospective multicentre review of patient registry Data from 37 centres from 18 countries who submitted data to a European Registry (SCETIDE) between 1968 and 1999	Patients with PID (SCID or non-SCID) Median age at HSCT is presented by donor type and ranges from 5.6 to 9.1 months for SCID and 17.5 to 40.7 months for non-SCID (ranges not reported)	n=919 (475 SCID 444 non-SCID) HSCT Median follow-up from HSCT is presented by donor type and ranges from 6 to 11 years for SCID and 4 to 9 years for non-SCID (range limits cover 0.7 years to 30 years)	Clinical effectiveness	Survival	**SCID** 3-year survival significantly better for HLA identical transplant (77%) than HLA-mismatched (54%) (p=0.002) In multivariate analysis for HLA-identical transplant there was a significant association between increased 3-year survival and age at transplantation <12 months (p=0.0002) and use of trimethoprim-sulphamethoxazole prophylaxis (p=0.002) In multivariate analysis for HLA-mismatched transplant there was a significant association between increased 3-year survival and B^+ SCID phenotype (p=0.0007), use of a protected environment (p=0.0001) and no pulmonary infection before	5	Direct	This uncontrolled retrospective review included patients from 37 European centres over a 31 year period and had a large sample size. Only risk factors that were significant in multivariate analysis were reported. The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the 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.

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**
						HSCT (p=0.0001) **Non-SCID 3-year survival:** • Genotypically HLA-matched 71% • Phenotypically HLA-matched 42% • HLA-mismatched related 42% • Unrelated-donor transplant 59% p=0.0006 No risk factors significant on multivariate analysis			
				Clinical effectiveness	Engraftment	In patients alive >1 month after HSCT **SCID** Sustained engraftment significantly better for HLA identical transplant (96%) than HLA-mismatched (90%) (OR 2.7 95%CI 1.2 to 7.4) **Non-SCID** • Genotypically HLA-matched 99% • Phenotypically HLA-matched 81% • HLA-mismatched related 75% • Unrelated-donor transplant 79% p=0.001			
				Safety	Safety	**Cause of death for SCID (n not reported)** • Infection 56% • GVHD 25% • B-cell lymphoproliferative syndrome 5% **Cause of death for non-SCID (n not reported)** • Infection 70% • GVHD 9% • Toxic effects of conditioning regimen 9% • B-cell lymphoproliferative syndrome			

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**
						5% • Rejection 3%			
Filipovitch et al (2001)	S2 – Retrospective multicentre review of patient registry Data submitted to the International Bone Marrow Transplant Registry and/or national Marrow Donor Program from 60 centres between 1968 and 1996	Patients with WAS Median age at HSCT is presented by donor type and ranges from 2 to 3 years (range 1-32 years)	n=170 HSCT Median follow-up 42 months (range 2 to 304)	Clinical effectiveness	Survival	5-year survival 70% (95%CI 63 to 77) In multivariate analysis, decreased survival was significantly associated with use of related donors, other than HLA-identical siblings, regardless of recipient age (p=0.0004) and use of unrelated donors in patients >5 years old (p=0.001)	5	Direct	This uncontrolled retrospective review included patients from 60 worldwide centres over a 28 year period and had a moderate sample size. Risk factors included in multivariate analysis included donor type, age at HSCT, Lansky/Karnofsky performance scores before HSCT, infection prior to conditioning, donor-recipient HLA disparity, donor sex, type of conditioning regimen, type of GVHD prophylaxis and year of HSCT. The retrospective design of the study introduces the possibility of selection bias in the study population. This can result from the reporting of patient details to the database, the patients included in the analysis and the 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.
				Clinical effectiveness	Engraftment	For 87 patients with data available, 89% had documented donor cell engraftment after the 1st HSCT			
				Clinical effectiveness	Immuno-logic reconstitution	91% achieved haematopoietic recovery after 1st HSCT (data available for 154 patients surviving ≥28 days after HSCT) 7 patients had graft failure after initial haematopoietic recovery			
				Clinical effectiveness	Requirement for more than one HSCT	20 (14%) had >1 HSCT			
				Clinical effectiveness	Activity of daily living	Activity of daily living assessed by Karnofsky/ Lansky age performance scores Data available for 61 patients between 2 and 14 years after HSCT. Lowest performance scores in that period were: • 100% score: 84% • 90% score: 13% • 80% score: 2% • 20% score: 2%			

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**
				Clinical effectiveness	Centre assessment	Post-transplantation status of 120 surviving patients: • Cured 53% • Improved 18% • Unchanged 3% • Worse 3% • Not reported 23%			
				Safety	Safety	Cause of death (n=50) • GVHD 22% • Infection 20% • Graft failure 12% • Malignancy 12% • Organ failure 8% • Haemorrhage 8% • Interstitial pneumonitis 6% • Unknown 12% Acute grade II-IV GVHD (in patients surviving >21 days after HSCT): 36% (58/160) Chronic GVHD (in patients surviving ≥90 days after HSCT): 23% (33/141)			

ADA – adenosine deaminase; ADHD – attention deficit hyperactivity disorder; CGD- chronic granulomatous disease; CI – confidence interval; GERD – gastroesophageal reflux disorder; GVHD – graft versus host disease; HLA – human leukocyte antigens; HLH – haemophagocytic lymphohistiocytosis; HSCT – haematopoietic stem cell transplant; ICU – intensive care unit; IgM – Immunoglobulin M; IVIG – immunoglobulin intravenous; mAb – monoclonal antibody; MMRDT – mismatched related donor transplantation; OR – odds ratio; PICU – paediatric intensive care unit; PID – primary immune deficiency; PTLD –EBV – post-transplant lymphoproliferative disease-Epstein-Barr virus associated; SCETIDE – Stem Cell Transplantation for Immunodeficiencies; SCID – severe combined immune deficiency; UCBT – umbilical cord blood transplantation; WAS – Wiskott-Aldrich syndrome

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	Moratto et al (2011)	7	Direct	B	Overall survival is the proportion of patients alive at last follow-up. In the highest scoring of the studies (Moratto et al 2011), overall survival was 82% (no confidence intervals reported). In multivariate analysis, better survival was associated with HSCT after the year 2000 ($p<0.05$) and reduced survival was associated with the use of a mismatched[30] family donor or cord blood ($p<0.05$). This study included patients with WAS. The median age at HSCT was 34.6 months (range 2 to 240 months) with a median follow-up of 76.8 months or 6.4 years (range 12 to 346 months). A high overall survival rate in the context of a life-threatening condition is a positive outcome. However, a longer median follow-up period would give better evidence about the impact on survival. This uncontrolled retrospective review included patients from 12 European and American centres treated over a 29 year period to 2009, and had a moderate sample size (n= 194). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
	de la Morena et al (2017)	6	Direct		
	Schuetz et al (2014)	6	Direct		
	Cole et al (2012)	6	Direct		
	Hassan et al (2012)	6	Direct		
	Railey et al (2009)	6	Direct		
Fixed-term survival	Mitchell et al (2013)	7	Direct	A	Fixed-term survival is the proportion of patients alive at a specified interval. In Mitchell et al (2013), (which has the broader population group i.e. any PID of the 2 highest scoring studies) the 5-year survival was 72% (no confidence intervals reported). In multivariate analysis, decreased survival was significantly associated with active cytomegalovirus disease, interstitial pneumonitis and veno-occlusive disease ($p<0.05$). 5-year survival for the most common PIDs was 70% for SCID, 81% for WAS and 69% for CGD. This study included patients with any PID. The median age at HSCT was 1 year (range 0-15 years) with a median follow-up of 6 years (range 0.39 to 17.31 years). A high overall survival rate in the context of a life-threatening condition is a positive outcome. However, a longer median follow-up period would give better evidence about the impact on survival. This uncontrolled retrospective review included patients from 6 centres in Australia and New Zealand treated over a 17 year period to 2008, and had a moderate sample size (n= 135). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
	Moratto et al (2011)	7	Direct		
	Heimall et al (2017)	6	Direct		
	Pai et al (2014)	6	Direct		
	Fernandes et al (2012)	6	Direct		
	Gennery et al (2010)	6	Direct		
	Railey et al (2009)	6	Direct		
	Trottestam et al (2011)	5	Direct		
	Antoine et al (2003)	5	Direct		
	Filipovitch et al (2001)	5	Direct		
Long term survival > 2 years after HSCT	Eapen et al (2012)	5	Direct	C	Long term survival more than 2 years after HSCT is the proportion of patients who survived at least 2 years after HSCT who were still alive at last follow-up. In Eapen et al (2012), 7-year survival amongst patients who had survived at least 2 years

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

Use of allogeneic HSCT for PID (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					after HSCT was 93% (95%CI 89 to 97) for SCID patients and 96% (95%CI 94 to 98) for non-SCID patients. 9-year survival was 92% for SCID and 96% for non-SCID (confidence intervals not reported). Median age at HSCT was not reported in this study; however 97% of SCID and 63% of non-SCID were less than 2 years old. The median follow-up was 7.8 years for SCID and 6.3 years for non-SCID. The survival rates of over 90% reported in this study suggest that most patients who survive the first 2 years after HSCT have a positive survival outcome. A longer median follow-up period would give better evidence about the impact on survival. This uncontrolled retrospective review included patients from 114 worldwide centres treated over a 23 year period to 2003, and had a large number of PID patients (n= 606). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
Transplant-related mortality	Mitchell et al (2013)	7	Direct	B	Transplant-related mortality was defined as death from any cause other than persistent disease (Mitchell et al 2013). In the highest scoring study (Mitchell et al 2013) the cumulative incidence of transplant-related mortality at 100 days was 10%. At 1-year this was 22%. In multivariate analysis, increased risk of transplant-related mortality was significantly associated with active cytomegalovirus disease, interstitial pneumonitis and veno-occlusive disease. This study included patients with any PID. The median age at HSCT was 1 year (range 0-15 years) with a median follow-up of 6 years (range 0.39 to 17.31 years). The transplant-related mortality rate of 22% at 1-year reflects the seriousness of PID and the risks associated with HSCT. A number of risk factors for early mortality after HSCT were identified. This uncontrolled retrospective review included patients from 6 centres in Australia and New Zealand treated over a 17 year period to 2008, and had a moderate sample size (n= 135). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
	Hassan et al (2012)	6	Direct		
Relative mortality rate	Eapen et al (2012)	5	Direct	C	Relative mortality is the relative risk of dying at a given time after transplantation as compared with a person of similar age, sex, and nationality in the general population (Eapen et al 2012). Excess deaths per 1,000 compared to an age, sex and nationality matched population was 54 (95%CI 28 to 79) for SCID and 38 (95%CI 25 to 51) for non-SCID for 2-6 years after HSCT. In 6-10 years after HSCT there was no significant difference in mortality risks for surviving patients compared to the general population. Median age at HSCT was not reported in this study; however 97% of SCID and 63% of non-SCID were less than 2 years old. The median follow-up was 7.8 years for SCID and 6.3 years for non-SCID. The lack of difference in mortality risk compared to the general population beyond 6 years suggests that long term outcomes for those patients who survive the first few years after HSCT are positive, although it may also reflect the smaller

Use of allogeneic HSCT for PID (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					number of patients for whom longer term data are available. This uncontrolled retrospective review included patients from 114 worldwide centres treated over a 23 year period to 2003, and had a large number of PID patients (n= 606). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
Engraftment	Mitchell et al (2013)	7	Direct	A	Engraftment occurs when the stem cells of the donor have been taken up by the patient's bone marrow and produce new blood and immune system cells. Neutrophil engraftment was defined as the first of 3 consecutive days of absolute neutrophil count of ≥0.5x10^9/L and platelet engraftment was defined as a platelet count of ≥20x10^9/L measured a minimum of 7 days after the last platelet transfusion (Mitchell et al 2013). In Mitchell et al (2013), (which has the broader population group i.e. any PID of the 2 highest scoring studies), neutrophil engraftment was 89% with a median time to engraftment of 16 days (range 1-62) and platelet engraftment was 85% with a median time to engraftment of 30 days (range 1-112). The median age at HSCT was 1 year (range 0-15 years) with a median follow-up of 6 years (range 0.39 to 17.31 years). High levels of engraftment are a positive outcome for HSCT, indicating the successful uptake of donor cells. This uncontrolled retrospective review included patients from 6 centres in Australia and New Zealand treated over a 17 year period to 2008, and had a moderate sample size (n= 135). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
	Moratto et al (2011)	7	Direct		
	de la Morena et al (2017)	6	Direct		
	Pai et al (2014)	6	Direct		
	Fernandes et al (2012)	6	Direct		
	Hassan et al (2012)	6	Direct		
	Antoine et al (2003)	5	Direct		
	Filipovitch et al (2001)	5	Direct		
Immunologic reconstitution	Moratto et al (2011)	7	Direct	B	Immunologic reconstitution outcomes include the normalisation of T and B lymphocytes and T lymphocyte subsets ($CD3^+$>1,000, $CD4^+$>600, $CD8^+$>300, $CD19^+$>200 cells/μL) and the requirement for intravenous immunoglobulin (IVIG) after HSCT. The highest scoring of the studies (Moratto et al 2011) reported immunologic reconstitution ≥12 months after HSCT. 68% of patients showed normalisation of the absolute count of T and B lymphocytes and of T lymphocyte subsets and 13% required IVIG. This study included patients with WAS. The median age at HSCT was 34.6 months (range 2 to 240 months) with a median follow-up of 76.8 months or 6.4 years (range 12 to 346 months). A majority of patients achieved normalisation, but some still required IVIG. This uncontrolled retrospective review included patients from 12 European and American centres treated over a 29 year period to 2009, and had a moderate sample size (n= 194). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
	Heimall et al (2017)	6	Direct		
	Pai et al (2014)	6	Direct		
	Schuetz et al (2014)	6	Direct		
	Fernandes et al (2012)	6	Direct		
	Hassan et al (2012)	6	Direct		
	Railey et al (2009)	6	Direct		
	Filipovitch et al (2001)	5	Direct		
Chimerism	Moratto et al (2011)	7	Direct	B	Chimerism relates to the presence of donor cells after transplantation. Mixed chimerism is a combination of patient and donor cells. In full chimerism only donor cells are present. Low chimerism was defined as 5% to 50% of donor cells. Null chimerism was defined as <5% donor cells (Moratto et al 2011).
	Pai et al (2014)	6	Direct		
	Fernandes et al (2012)	6	Direct		

Use of allogeneic HSCT for PID (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					In the highest scoring of the studies (Moratto et al 2011), 28% showed mixed chimerism in at least one of the cell lineages tested (T lymphocytes, B lymphocytes, myeloid cells). Low or null donor chimerism was more common within myeloid cells (16.5%) than in B lymphocytes (7.4%) or T lymphocytes (3.2%). This study included patients with WAS. The median age at HSCT was 34.6 months (range 2 to 240 months) with a median follow-up of 76.8 months or 6.4 years (range 12 to 346 months). Mixed chimerism after HSCT for WAS has been reported to be associated with increased risk of autoimmunity[31] (Moratto et al 2011). This uncontrolled retrospective review included patients from 12 European and American centres treated over a 29 year period to 2009, and had a moderate sample size (n= 194). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
Requirement for more than one HSCT	Mitchell et al (2013)	7	Direct	B	Further transplantation can be required due to graft failure or rejection. In the highest scoring study (Mitchell et al 2013) 18 (13%) patients required a 2nd HSCT. This study included patients with any PID. The median age at HSCT was 1 year (range 0-15 years) with a median follow-up of 6 years (range 0.39 to 17.31 years). A relatively low proportion of patients required a 2nd HSCT. This uncontrolled retrospective review included patients from 6 centres in Australia and New Zealand treated over a 17 year period to 2008, and had a moderate sample size (n= 135). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
	Heimall et al (2017)	6	Direct		
	de la Morena et al (2017)	6	Direct		
	Pai et al (2014)	6	Direct		
	Fernandes et al (2012)	6	Direct		
	Cole et al (2012)	6	Direct		
	Railey et al (2009)	6	Direct		
	Filipovitch et al (2001)	5	Direct		
Admission to intensive care	Cole et al (2012)	6	Direct	C	Complications after HSCT can lead to an admission to paediatric or adult intensive care (ICU) where support can be provided for failing organ systems such as ventilation, cardiovascular support and renal replacement therapy (Cole et al 2012). 35% of patients required at least one ICU admission at a median of 31 days after HSCT for the 1st admission (range -6 to 834). The most common reason for admission was respiratory problems (59%). Other reasons included surgical problems (17%), complications related to veno-occlusive disease (9%), cardiovascular instability (5%), infection (5%) and neurological problems (5%). The median duration of admission was 6 days (range 1-35). This study included patients with any PID. The median age at HSCT was 1 year 4 months (range 1 month to 19 years 4 months. The follow-up period was not reported. The fact that more than a third of patients required an ICU admission reflects the serious, life-threatening nature of PID and the risks associated with HSCT. This uncontrolled retrospective review included patients treated at 1 UK centre over a 5

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

Use of allogeneic HSCT for PID (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					year period to 2009, and had a moderate sample size (n= 111). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
Post-transplant malignancy	Kamani et al (2011)	7	Direct	B	Post-transplant malignancy was defined as the development of a new malignancy after HSCT (Kamani et al 2011). Only cases confirmed by pathology reports and/or confirmed with the transplant centre were included. 52 (2.3%) of patients developed a confirmed post-transplant malignancy, of whom 40 had died at follow-up. The cumulative incidence of malignancy was 2% (95%CI 2 to 3) at 5-years; 2% (95%CI 2 to 3) at 10-years and 3% (95%CI 2 to 5) at 15 years. The cumulative incidence was higher in WAS patients (4%, 95%CI 2 to 6 at 5, 10 and 15 years) than SCID patients (2%; 95%CI 1 to 3 at 5 and 10 years and 3%; 95%CI 1 to 6 at 15 years). Lymphoproliferative disorders were the most common malignancy, occurring in 45 patients (87%) with a median time to development of 3 months after HSCT (range 1-41). This study included patients with any PID. The median age at HSCT was 1 year (range 1.2 months to 47 years) with a median follow-up of 6 years (range 4 to 14). Kamani et al report that the overall risk of cancer in children with PID is estimated to be 4%. This uncontrolled retrospective review included patients treated at over 500 centres worldwide over a 35 year period to 2003, and had a large sample size (n= 2,266). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
Activities of daily living	de la Morena et al (2017)	6	Direct	B	Karnofsky/ Lansky scores were reported for patients that did and did not receive an HSCT. Karnofsky/ Lansky scores are used to determine functional status. The Karnofsky Scale is designed for people aged ≥16 years and the Lansky Scale is designed for people <16 years old. Both Scales are scored from 10 to 100. Higher scores indicate better function (CIBMTR 2009). In the highest scoring study (de la Morena et al 2017) surviving patients treated with HSCT had higher median scores (100%) than patients who did not receive HSCT (90%) at last follow-up ($p<0.001$). This study included patients with X-linked hyper IgM syndrome and had a mean follow-up of 8.5 ± 7.2 years. The median age at HSCT was 2.9 years (range 0.1 to 24). A score of 100% is defined as “normal, no complaints, no evidence of disease” on the Karnofsky Scale and “fully active” on the Lansky Scale. A score of 90% is defined as “able to carry on normal activity” on the Karnofsky Scale and “minor restriction in physically strenuous play” on the Lansky Scale. This uncontrolled retrospective review included patients treated at 28 centres worldwide over a 49 year period to 2013, and had a moderate sample size (n= 176). Although results are presented for patients who did and did not receive HSCT it is not a comparative study. Reasons why patients did not receive HSCT are not reported. The retrospective design and lack of controlled comparator limit the strength of the conclusions that can be drawn.
	Filipovitch et al (2001)	5	Direct		

Use of allogeneic HSCT for PID (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Quality of life	Railey et al (2009)	6	Direct	C	Quality of life was assessed using a non-validated SCID-specific questionnaire developed by the study authors (Railey et al 2009) and sent to the families of 111 surviving patients during the study follow-up period (timings not reported). 86% of patients were considered to be healthy by their families, with 36% reporting no health problems in the last 2 years. Where health problems were reported the most common (affecting ≥10%) were persistent rash (25%), sinusitis (20%), asthma (14%), diarrhoea (14%), ADHD (21%) and developmental delay (10%). 12% of patients were below the 3rd percentile for height and weight and 3% required special schooling. This study included patients with SCID who did not receive pre-transplant chemotherapy or post-transplant GVHD prophylaxis and had a median follow-up of 8.7 years (range 2.9 to 14.1). Age at HSCT was not reported. A high proportion of the surviving patients were considered healthy by their families. This uncontrolled retrospective review included patients treated at 1 US centre over a 16 year period to 2008, and had a moderate sample size (n= 161). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
Centre assessment	Filipovitch et al (2001)	5	Direct	C	Centres' assessment of post-HSCT outcome for surviving patients related to the underlying WAS disease. No definitions for the categories used were reported. 53% of patients were considered 'cured', 18% 'improved', 3% 'unchanged' and 3% 'worse'. Status was not reported for 23%. This study included patients with WAS and had a median follow-up of 42 months (range 2 to 304). 71% of the 120 surviving patients were considered 'cured' or 'improved'. However data was missing for 23% of surviving patients. This uncontrolled retrospective review included patients treated at 60 worldwide centres over a 28 year period to 1996, and had a moderate sample size (n= 170). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
Safety	Mitchell et al (2013)	7	Direct	A	Safety outcomes include cause of death, adverse events and GVHD. In GVHD the donated cells react against the patient's body which can lead to an immune response attack. GVHD is graded as I – mild; II – moderate; III – severe; IV – life threatening. In Mitchell et al (2013), (which has the broader population group i.e. any PID of the 2 highest scoring studies and detailed reporting on safety outcomes) 36 patients (27%) died. Cause of death included infection (22%), interstitial pneumonitis (non-infectious) (17%), GVHD (14%), graft failure (14%), organ failure (14%), haemorrhage (11%) and acute respiratory syndrome (non-infectious) (8%). Adverse events after HSCT included cytomegalovirus (19%), interstitial pneumonitis (15%), veno-occlusive disease (13%) and haemorrhagic cystitis (4%). The 100 day cumulative incidence for acute GVHD (grade II to IV) was 25%. The 1-year cumulative incidence for chronic GVHD was 16%. In multivariate analysis decreased risk of GVHD was significantly associated with the use of a fully
	Moratto et al (2011)	7	Direct		
	Kamani et al (2011)	7	Direct		
	Heimall et al (2017)	6	Direct		
	de la Morena et al (2017)	6	Direct		
	Pai et al (2014)	6	Direct		
	Schuetz et al (2014)	6	Direct		
	Fernandes et al (2012)	6	Direct		

Use of allogeneic HSCT for PID (no comparator)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
	Hassan et al (2012)	6	Direct		matched sibling donor and HSCT performed after 1998 (p=0.002).
	Railey et al (2009)	6	Direct		This study included patients with any PID. Median follow-up was 6 years (range 0.39 to 17.31 years). The number of deaths and adverse events reported reflects the seriousness of PID and the risks associated with HSCT. A number of risk factors significantly associated with the incidence of GVHD were identified.
	Eapen et al (2012)	5	Direct		
	Trottestam et al (2011)	5	Direct		
	Antoine et al (2003)	5	Direct		This uncontrolled retrospective review included patients from 6 centres in Australia and New Zealand treated over a 17 year period to 2008, and had a moderate sample size (n= 135). The retrospective design and lack of comparator limit the strength of the conclusions that can be drawn.
	Filipovitch et al (2001)	5	Direct		

ADHD – attention deficit hyperactivity disorder; CGD- chronic granulomatous disease; CI – confidence interval; GVHD – graft versus host disease; HLA – human leukocyte antigens; HLH – haemophagocytic lymphohistiocytosis; HSCT – haematopoietic stem cell transplant; ICU – intensive care unit; IgM – Immunoglobulin M; IVIG – immunoglobulin intravenous; PID – primary immune deficiency; SCID – severe combined immune deficiency; WAS – Wiskott-Aldrich syndrome

9 Literature Search Terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there sub-groups that need to be considered?	All patients with primary immunodeficiencies: children and adults
I – Intervention Which intervention, treatment or approach should be used?	Allogeneic haematopoietic stem cell transplant (HSCT)
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Current treatments include: • Ongoing antimicrobial therapy • Therapy with antibodies • Biological modifying drugs • Immunoglobulin (IVIg) replacement therapy • Systemic immunosuppressive therapy (for auto-inflammatory/ immune dysregulation complications) • Broad spectrum antimicrobials (including anti-virals and anti-fungals)
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.	All outcome measures reported in included studies <u>Critical to decision-making:</u> • Survival • Infection rate • 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
Assumptions / limits applied to search	
Inclusion criteria: • Peer-reviewed publications in the English Language • 2000 to present • All ages • Randomised studies, non-randomised prospective cohort studies, case-control studies, case series including at least 4 subjects	

10 Search Strategy

We searched PubMed, Embase and Cochrane Library limiting the search to papers published in England from **1St January 2000 to 1st December 2017**. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 1st December 2017
Embase search:

# ▲	Searches	Results
1	((primary or innate or inherited) adj (immun?deficienc* or immun* deficienc*)).ti,ab.	7577
2	((combined or adenosine deaminase or common variable) adj (immun?deficienc* or immun* deficienc*)).ti,ab.	11124
3	recombinant activating gene*.ti,ab.	10
4	wiskott aldrich syndrome?.ti,ab.	2680
5	(hyper igm or hyper ige).ti,ab.	1984
6	((ligand or ctla4 or cytotoxic t-lymphocyte* or xiap or x-linked inhibitor or iap3 or birca4 or antibod*) adj3 deficien*).ti,ab.	3508
7	(chronic granulomatous adj (disease? or disorder?)).ti,ab.	4539
8	((hemophagocytic or haemophagocytic) adj lymphohistiocytosis).ti,ab.	3522
9	(phagocytic cell adj (disease or disorder?)).ti,ab.	6
10	combined immunodeficiency/ or common variable immunodeficiency/ or exp severe combined immunodeficiency/ or wiskott aldrich syndrome/	15519
11	phagocyte dysfunction/ or chronic granulomatous disease/ or hyper ige syndrome/	6241
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	37463
13	exp bone marrow transplantation/	62661
14	allotransplantation/	34299
15	((bone marrow or allo* or h?ematopoietic or h?emopoietic) adj3 transplant*).ti,ab.	115253
16	(allo hsct or ahsct or hsct or bmt).ti,ab.	35392
17	13 or 14 or 15 or 16	170670
18	12 and 17	4757
19	(exp animals/ or nonhuman/) not human/	6422739
20	18 not 19	4502
21	(conference* or editorial or letter or note or "review").pt. or case report/	9985045
22	20 not 21	1367
23	limit 22 to (english language and yr="2000 -Current")	884
24	limit 20 to "reviews (maximizes specificity)"	9
25	23 or 24	890

A supplemental search to check for additional studies using additional specific terms did not identify any new studies.

# ▲	Search 2	Results
1	recombination activating gene.ti,ab.	741
2	((cd40 or cd-40 or cd152 or cd-152) adj3 deficien*).ti,ab.	341
3	1 or 2	1081
4	exp bone marrow transplantation/	62706
5	allotransplantation/	34310
6	((bone marrow or allo* or h?ematopoietic or h?emopoietic) adj3 transplant*).ti,ab.	115412
7	(allo hsct or ahsct or hsct or bmt).ti,ab.	35442
8	4 or 5 or 6 or 7	170862
9	3 and 8	79
10	(exp animals/ or nonhuman/) not human/	6429836
11	9 not 10	51
12	(conference* or editorial or letter or note or "review").pt. or case report/	10004236
13	11 not 12	19
14	limit 13 to (english language and yr="2000 -Current")	19

11 Evidence Selection

- Total number of publications reviewed: 158
- Total number of publications considered potentially relevant: 49
- Total number of publications selected for inclusion in this briefing: 16

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