UK National Screening Committee

# Screening for Severe Combined Immunodeficiency

## External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: 3

**Bazian Ltd**

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

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# Introduction

### Severe Combined Immunodeficiency (SCID)

Severe combined immunodeficiency (SCID) is a group of disorders characterized by the absence of humoral and cellular immunity.[1] It can be caused by mutations in a number of different genes.[2] Left untreated, it is fatal in early childhood, due to the development of common and opportunistic infections.[3,4] However, there are several treatment options available. The main treatment option is haematopoietic stem cell transplant (HSCT), although enzyme replacement therapy and gene therapy can be used to treat certain subtypes of SCID. There is evidence that early treatment, prior to the acquisition of infections is associated with the highest survival rates.

### Current policy

There is no current policy on newborn screening for SCID

### This report

In 2010 SCID was included in the US newborn screening core panel. This report uses the systematic evidence review prepared for the US Advisory Committee on Heritable Disorders in Newborns and Children and the abridged version published in 2010, in combination with evidence published between October 2008 (the upper limit of the systematic search performed for these reports) and 2011.[1,4] Newborn screening for SCID was assessed against the UK National Screening Committee (NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme (National Screening Committee 2003).

Particular areas of interest identified by the National Screening Committee included:

- The prevalence of SCID in the UK
- The T cell receptor excision circle (TREC) screening test, particularly:
    - Cut-off values
    - Timing of the test
    - The practicality of PCR as a screening technology
    - The false negative rate
    - Information on children identified by the test with other T cell lymphopenias
- Treatment, especially if screen detection improves survival
- The Screening program, including:
    - Quality Assurance measures
    - Follow-up rearrangements for screen positive babies

For this review an updated systematic search has been performed for relevant publications from 2002 to the end of 2011. Overall, 361 citations were judged to be relevant (see Methodology section for study breakdown).

Publications published since October 2008 were considered, since this was the upper limit of the systematic search performed for the evidence reviews for the US Advisory Committee on Heritable Disorders in Newborns and Children.[1,4] The full text of selected papers were retrieved

after a first pass appraisal at abstract level. In a similar manner to the systematic evidence reviews, non-systematic reviews, editorials, other opinion pieces, reports of case series of fewer than four patients, articles with only adult subjects, and those with nonhuman data were excluded. Studies of immunodeficiencies not designated as SCID by The International Union of Immunological Societies Expert Committee for Primary Immunodeficiency (2011) were not included.[2] Additional relevant references identified during the preparation of the report were also included. An overview of the most informative and relevant references regarding the individual screening criteria is given below.

## Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

### 1. The condition should be an important health problem

Severe combined immunodeficiency (SCID) is a group of disorders characterized by the absence of humoral and cellular immunity.[1] It can be caused by mutations in a number of different genes.[2] Left untreated, it is fatal in early childhood, due to the development of common and opportunistic infections.[3,4] (see Criterion 2) However, there are several treatment options available. The main treatment option is haematopoietic stem cell transplant (HSCT), although enzyme replacement therapy and gene therapy can be used to treat certain subtypes of SCID.

The vignette produced by Professor Bobby Gaspar states that in 2008 and 2009, 20 children per year presented with SCID to the two UK centres for care (Great Ormond Street Hospital and Newcastle General Hospital). This suggests an incidence of approximately 1 in 35,000 (or 2.86 per 100,000).[5] However, this does not take into account children who may have been diagnosed after death at other UK centres or children with the disease that die undiagnosed.

There is evidence that early diagnosis and treatment is associated with the highest survival rates. A UK study, Brown et al. (2011), compared survival in infants who were diagnosed early due to a family history of SCID with the first presenting family member, in children diagnosed between 1979 and 2010 and treated at Great Ormond Street Hospital or Newcastle General Hospital.[6] The median age of diagnosis in children who were the first presenting member was 143.5 days. Overall survival in this group was 40%: 17 of 48 children died before HSCT could be performed, and 12 of the 31 children who had HSCT died after the transplant (median follow-up not reported). In contrast, siblings were diagnosed earlier, with four children diagnosed antenatally and the median age of diagnosis in the remaining cohort was 0 days (at birth). Survival in the sibling cohort was 90%, with only one death prior to HSCT and five deaths in the 59 children who received HSCT or gene therapy (median follow-up not reported).[6] The benefits of treatment are discussed further in Criterion 10.

**Summary: Criterion 1 Met**

**Severe combined immunodeficiency is as an important health problem. If left untreated the disease is invariably fatal. Children may die before diagnosis or treatment, of those that survive to receive HSCT or gene therapy, cure is possible. SCID is a rare condition and recent estimates suggest that approximately 2.86 infants per 100,000 (1 in 35,000 infants) are diagnosed with the condition in the UK each year.**

## 2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

**Epidemiology**

SCID is "a group of disorders characterized by the absence of humoral and cellular immunity."[1] SCID is a disorder of T cell development, which can be caused by mutations in a number of different genes.[7] Depending on the mutation, B cell and natural killer (NK) cells development can also be severely compromised in SCID. SCID is often classified by the combination of T/B/NK cells present.[7] The International Union of Immunological Societies Expert Committee for Primary Immunodeficiency published an update on the classification of primary immunodeficiency in 2011.[2] They classify SCID as part of combined immunodeficiency, and list six types of T-B+ SCID and five types of T-B-SCID (Table 1). However, other publications and experts consider that SCID can be caused by mutations in other genes. For example, Cossu (2010) lists 30 subtypes of SCID.[7]

**Table 1 | Combined immunodeficiencies.**

| Disease | Circulating T cells | Circulating B cells | Serum Ig | Associated features | Inheri-tance | Genetic defect/ presumed pathogenesis | OMIM number |
|---|---|---|---|---|---|---|---|
| **1. $T^-B^+$ Severe combined immunodeficiency (SCID)** | | | | | | | |
| (a) γc deficiency | Markedly decreased | Normal or increased | Decreased | Markedly decreased NK cells; leaky cases may present with low to normal T and/or NK cells or Omenn syndrome | XL | Defect in γ chain of receptors for IL-2, -4, -7, -9, -15, -21 | 300400 |
| (b) JAK3 deficiency | Markedly decreased | Normal or increased | Decreased | Markedly decreased NK cells; leaky cases may present with variable T and/or NK cells | AR | Defect in Janus activating kinase 3 | 600173 |
| (c) IL7Rα deficiency | Markedly decreased | Normal or increased | Decreased | Normal NK cells | AR | Defect in IL-7 receptor α chain | 146661 |
| (d) CD45 deficiency* | Markedly decreased | Normal | Decreased | Normal γ/δ T cells | AR | Defect in CD45 | 151460 |
| (e) CD3δ*/ CD3ε*/CD3ζ* deficiency | Markedly decreased | Normal | Decreased | Normal NK cells No γ/δT cells | AR | Defect in CD3δ, CD3ε, or CD3ζ chains of T cell antigen receptor complex | 186790, 186830, 186740 |
| (f) Coronin-1A deficiency* | Markedly decreased | Normal | Decreased | Detectable thymus | AR | Defective thymic egress of T cells and defective T cell locomotion | 605000 |
| **2. $T^-B^-$ SCID** | | | | | | | |
| (a) RAG 1/2 deficiency | Markedly decreased | Markedly decreased | Decreased | May present with Omenn syndrome, expanded γ/δT cells, autoimmunity, and/or granulomas | AR | Defective VDJ recombination; defect of recombinase activating gene (RAG) 1 or 2 | 601457 |
| (b) *DCLRE1C* (Artemis) deficiency | Markedly decreased | Markedly decreased | Decreased | Defective VDJ recombination, radiation sensitivity; may present with Omenn syndrome | AR | Defective VDJ recombination; defect in Artemis DNA recombinase repair protein | 602450 |
| (c) DNA-PKcs deficiency* | Markedly decreased | Markedly decreased | Decreased | (Widely studied *scid* mouse defect) | AR | Defective VDJ recombination; defect in DNA-PKcs recombinase repair protein | 600899 |
| (d) Reticular dysgenesis, AK2 deficiency | Markedly decreased | Decreased or normal | Decreased | Deficiency of T, B, and NK cells with granulocytopenia, deafness | AR | Defective maturation of lymphoid and myeloid cells (stem cell defect) defect in mitochondrial adenylate kinase 2 | 103020 |
| (e) Adenosine deaminase (ADA) deficiency | Absent from birth (null mutations) or progressive decrease | Absent from birth of progressive decrease | Progressive decrease | Decreased NK cells, often with costochondral junction flaring, neurological features, hearing impairment, lung, and liver manifestations; partial ADA deficiency may lead to delayed or milder presentation | AR | Absent ADA activity, elevated lymphotoxic metabolites (dATP, *S*-adenosylhomocysteine) | 102700 |

**Table 1: Different forms of SCID. From Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency.[2] Abbreviations: XL, X-linked; AR, autosomal recessive.**

The European Society of Immunodeficiencies (ESID) state that SCID can be definitively diagnosed in patients less than two years of age with either engraftment of trans-placental-acquired maternal T cells; or less than 20% CD3+ T cells, an absolute lymphocyte count of less than 3000/$mm^3$ and either a mutation in the cytokine common gamma chain, mutation in JAK3,

mutation in RAG1 or RAG2, mutation in IL-7Rα or ADA activity of less than 2% of control or mutations in both alleles of ADA. SCID is probable in patients less than two years of age with less than 20% CD3+ T cells, an absolute lymphocyte count of less than 3000/$mm^3$ and proliferative responses to mitogens less than 10% of control; or in patients with maternal lymphocytes in the circulation.[3]

In Lipstein et al. (2010), a systematic review of newborn screening and treatment of SCID, they state that "the reported incidence of SCID is ~1 in 100,000 live births, but this may be an underestimate due to some children dying before diagnosis or having unrecognized less severe disease."[1] Two national studies published since 2008 (the search limit of the search for the systematic review was October 2008) were identified.

Yee et al. (2008) described the results of the Australian Paediatric Surveillance Unit study, carried out between May 1995 and December 2001.[8] During this time, 33 incident cases of SCID were identified, giving an incidence of 1.8 cases per $10^5$ births per annum. Twenty-six children had classical SCID (1.45 cases per $10^5$ live births). The median age at diagnosis of classical SCID was 6 months (range 0-20 months). Twenty-one (81%) children with classical SCID received HSCT; the median age at treatment was 9.8 months (range 1 to 36 months). Three children died between 1 and 4 months after transplantation, and one other child died whilst waiting for HSCT.[8]

The French national registry of primary immunodeficiencies (CEREDITH) have published the prevalence of primary immunodeficiency diseases between November 2005 and April 2009.[9] The prevalence of primary immunodeficiency diseases in the French national registry is estimated at 4.4 per 100,000 inhabitants. The prevalence of T cell deficiency diseases is estimated at 1.42 per 100,000 inhabitants. The prevalence of SCID (classified according to the International Union of Immunological Societies' criteria) is estimated at 0.22 per 100,000 inhabitants. The features of patients with T cell deficiencies or SCID are shown in Table 2 and Table 3.

| | Number | Gender (% male) | Status (% alive) | Consanguinity (%) | Known mutations |
|---|---|---|---|---|---|
| T cell deficiencies | 1173 | 59.3 | 73.7 | 26.4 | 63.2 |
| SCID | 219 | 62.6 | 61.2 | 35.8 | 90.0 |

**Table 2: Features of patients with T cell deficiencies and SCID in the French national registry of primary immunodeficiencies.[9]**

| | Number | Median age at diagnosis (years) | Number | Median time to diagnosis (year) |
|---|---|---|---|---|
| T cell deficiencies | 1061 | 1.6 | 1003 | 0.6 |
| SCID | 203 | 0.4 | 201 | 0.2 |

**Table 3: Features of patients with T cell deficiencies and SCID in the French national registry of primary immunodeficiencies (continued).[9]**

Interim results from the US SCID pilot screening studies performed in California, Louisiana, Massachusetts, New York, Puerto Rico, Wisconsin and the Navajo Nation were collated for the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children.[10] This report

found that approximately 1 in 16,032 infants were diagnosed with some form of T cell deficiency, and that 1 in 68,000 infants had SCID.[10] The incidence of SCID varied between states, from 1 in 34,159 in New York to 1 in 161,707 in Massachusetts. The incidence of all T cell deficiencies (including SCID) identified by the screening ranged from 1 in 8,540 in New York to 1 in 44,750 in California.[10]

No studies on the prevalence and incidence of SCID in the UK were identified. The vignette produced by Professor Bobby Gaspar states that in 2008 and 2009, 20 children per year presented with SCID to the two UK centres for care (Great Ormond Street Hospital and Newcastle General Hospital- based on an internal audit). This suggests an incidence of approximately 1 in 35,000 (2.86 infants per 100,000**)**.[5] It also states that a retrospective survey at these two centres, going back to 1979, found that 314 children had been diagnosed with SCID. The number of children diagnosed with SCID increased decade by decade, which Professor Bobby Gaspar suggests either indicates that awareness and diagnosis of the condition has increased over time or that there are an increasing number of patients with SCID in the UK.[5]

**Epidemiology of different forms of SCID**

In the full evidence review prepared for the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, Lipstein et al. (2009) reported on the relative frequencies of the different genetic forms of SCID and whether there are distinctive characteristics of SCID associated with the different genotypes.[4] They included evidence from a 1997 case-series which presented the demographic, genetic and immunological features of 108 infants with SCID treated at Duke University Medical Centre in the US. The relative frequencies of the different genotypes are presented in Table 4.

| | SCID infants (n=108) | | SCID families (n=88) | |
|---|---|---|---|---|
| **Genotype** | **Number** | **Percent** | **Number** | **Percent** |
| γc deficiency (X-linked) | 49 | 45.4 | 37 | 42 |
| ADA deficiency (autosomal recessive) | 16 | 14.8 | 13 | 15 |
| Jak3 deficiency (autosomal recessive) | 8 | 7.4 | 5 | 6 |
| Autosomal recessive (not ADA or Jak3 deficiency) | 21 | 19.4 | 19 | 22 |
| Reticular Dysgenesis (AK2 deficiency, autosomal recessive) | 1 | 0.9 | 1 | <1 |
| Cartilage-hair hypoplasia* (autosomal recessive) | 1 | 0.9 | 1 | <1 |
| Unknown | 12 | 11.1 | 12 | 14 |

**Table 4: Relative frequencies of different SCID genotypes from an American case series. Taken from the full evidence review prepared for the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children.[4] The table depicts genotype in the 108 individual patients in the first set of columns, and in the 88 families of origin in the second set of columns (where siblings count as one unit). *Cartilage-hair hypoplasia is not considered a form of SCID by the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency[2] (see Table 1).**

In the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children report on that status of newborn screening for SCID, it states that "past reporting of the molecular type of SCID found that 48% of cases are X-linked (IL2RG mutation), making this the most common form of SCID."[10] The report presents the molecular type of SCID in the nine SCID cases identified so far in New York and California. Contrary to previous reports, SCID was only found to be X-linked in one case (11%), and was inherited in an autosomal recessive manner in six cases (66%) (see Table 5).

| Molecular Type of SCID* | Number of SCID cases (%) |
|---|---|
| IL-7Rα (autosomal recessive) | 2 (22%) |
| RAG-1 (autosomal recessive) | 2 (22%) |
| ADA (autosomal recessive) | 2 (22%) |
| IL2RG (X-linked) | 1 (11%) |

**Table 5: Molecular type of SCID cases in New York and California Pilots. From The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children report.[10] *The report states that the molecular typing on one case is pending, but molecular types of 7 of the 9 SCID cases are presented.**

The epidemiology of different forms of SCID was not analysed further in this report.

**Natural history**

Most newborns with SCID appear normal and healthy at birth, but fail to thrive and develop infections in the first months of life.[7] The ESID state that "patients with SCID usually develop failure to thrive and persistent diarrhoea, respiratory symptoms and/or thrush in the first 2 to 7 months of life. Pneumocystis pneumonia, significant bacterial infections and disseminated BCG infection are common presenting illnesses. Occasional patients do not have failure to thrive and are not recognized to have immunodeficiency until late in the first year of life. SCID is fatal in the first 2 years of life unless the patient is treated with extremely restrictive isolation, haematopoietic stem cell transplant or therapy that replaces the abnormal gene or gene product."[3]

In the full evidence review prepared for the Advisory Committee on Heritable Disorders in Newborns and Children they conclude that "1) with the exception of children diagnosed early in life, typically through prenatal testing initiated because of family history, most children are diagnosed after recurrent pulmonary infections or infections with opportunistic organisms; 2) this is true of all SCID subtypes, although the exact timing may vary; and 3) without treatment of the underlying immunodeficiency, children with SCID die in early childhood from infection."[4] They state that pulmonary and opportunistic infections, leading to early childhood death, as the key complications of untreated SCID.[4]

**Detectable risk factor or disease marker**

SCID is a disorder of T cell development, and is therefore characterised by a lack of naïve T cells. The determination of the presence or levels of a number of disease markers have been suggested as potential screening tests. The most studied test, and the one which had been extensively studied in pilot studies in the US, is the T cell receptor excision circle (TREC) assay. TRECs are small, episomal DNA circles produced during differentiation of T cells, and are therefore absent or present in low numbers in newborns with SCID.[11,12] Screening for SCID is discussed further in Criterion 5.

**Latent period before disease onset**

Although SCID is present at birth, most newborns with SCID appear normal and healthy at birth.[3] Instead, children fail to thrive and develop infections in the first months of life.[3] SCID is then diagnosed at a few months of age, as protection from maternally-derived placentally-transferred immunoglobulins wanes. The average age of diagnosis varies between studies: in the CEREDITH registry the median age of diagnosis was 0.4 years (4.8 months), whereas the median age at diagnosis of classical SCID was 6 months in the Australian Paediatric Surveillance Unit study.[8,9] A recent UK study found that patients without a family history of SCID were diagnosed at a median age of 143.5 days (range 1 to 455 days), whereas their siblings were diagnosed antenatally or at 0 days (range 0-29 days).[6] Diagnosis at birth could allow measures to be taken to prevent infection, and could potentially allow treatment to occur earlier. The benefits of early treatment are described in Criterion 10.

**Summary: Criterion 2 Partly met**

**The epidemiology and natural history of the condition has been well described. SCID, as a group of similar disorders, has underlying genetic defects and characteristic inheritance which are the subject of ongoing research. Major sub-groups have been defined based on the pattern of T cell and B cell depletion. SCID is estimated to affect 1 in 100,000 live births, although no studies on the prevalence and incidence of SCID in the UK were identified.**

**However, from an internal audit of the two UK centres of care, an incidence of 2.86 infants per 100,000 can be estimated. The true prevalence of SCID in the UK may only be found if a screening program is implemented, since SCID is a rare disease and there is the possibility that affected children die before diagnosis. A potential latent period exists between birth and the onset of infections during which the child may be asymptomatic. The median age at diagnosis is 143.5 days in the UK for those without a family history. However the impact of population screening will be less in subgroups such as those with a family history of SCID, who may be screened at birth. Consanguinity was present in about 36% of cases in some studies and may provide a group for whom a targeted (non-population based) testing strategy could be appropriate**.

## 3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

**Criterion 3 Not applicable. SCID is a genetic disease.**

## 4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

The screening test identifies individuals who are not producing T-cell receptor excision circles (TRECs), a marker of T cell development, rather than screening for the presence of a mutation. Therefore carriers will not be identified.

The presence of a family member with the disease could lead to the genetic testing of other members of the family and the identification of individuals carrying the mutation. For example, the identification of a male infant with X-linked SCID could lead to the identification of the mother and/or female siblings as carriers. This would also be the case if infants with SCID are identified due to presentation with symptoms, although more infants with SCID may be diagnosed if newborn screening is implemented (i.e. fewer infants may remain undiagnosed).

**Criterion 4 Not applicable. The screening test identifies individuals who are not producing a marker of T cell development (see Criterion 5).**

## 5. There should be a simple, safe, precise and validated screening test

The 2010 systematic evidence review of newborn screening and treatment of SCID, Lipstein et al. (2010), states that “at least 3 different methods of newborn screening for SCID have been proposed, including (1) lymphocyte counts, (2) quantitative polymerase chain reaction for T cell receptor excision circles (TRECs), pieces of DNA produced only by T cells, and (3) enzyme linked immunosorbent assay, most commonly for interleukin 7 (IL-7), the level of which is elevated in the absence of T cells.”[1]

They summarised the results of four studies that had analysed newborn screening tests for SCID:

| Author, Study Design | Population | Significant Findings |
|---|---|---|
| Chan and Puck[8] (2005), case-control study | 23 children with SCID, 2 children with non-SCID immunodeficiencies, and 242 anonymized newborn screening cards | Used DNA amplification of TRECs from dried blood spot; among the children known to have SCID, none had detectable levels of TRECs; the 2 children with non-SCID immunodeficiency had detectable TRECs; had several presumed false-positives in which $\beta$-actin (a DNA control) could be amplified but TRECs could not |
| Hague et al[18] (1994), case-control study | 135 total children: 45 children with SCID and 90 children without SCID | Used first available lymphocyte count; children with SCID had significantly lower levels of lymphocytes; unlike the 5 control children with low lymphocyte count, low lymphocyte count persisted in children with SCID |
| Hennewig et al[19] (2007), cohort study | 36 children with rotavirus gastroenteritis: 18 with SCID and 18 without SCID | Lymphocyte study; children with SCID were more likely to have a low white blood cell count, eosinophilia, relative lymphopenia, and absolute lymphopenia |
| McGhee et al[20] (2005), case-control study | 13 children with SCID and 183 anonymized newborn screening cards | Dried blood spot study; proposed a 2-tiered screening approach measuring IL-7 first and then TRECs in those samples with elevated IL-7 levels; for this study IL-7 and TRECs were evaluated separately, in part because only 1 test could be performed from some samples; elevated IL-7: 4 of 114 anonymous cards, 11 of 13 children with SCID; undetectable TRECs: 14 of 183 anonymous cards, 3 of 3 children with SCID |

**Table 6: Studies assessing newborn screening tests for SCID included in the Lipstein et al. systematic evidence review of newborn screening and treatment of SCID.[1]**

Since the systematic review was completed, pilot newborn screening for SCID trials in the US have published results, and screening for SCID has been included in US core newborn screening panel. The pilot studies all used the TREC assay to screen for SCID. Results of studies published using this test are summarised below.

**T cell receptor excision circles**

T cell receptor excision circles (TRECs) are small, episomal DNA circles produced during differentiation of T cells as a result of rearrangement of T cell receptor genes.[11-13] During T cell differentiation the T cell receptor genes are rearranged leading to the joining of the V, D and J gene segments of the T cell receptor. TRECs are generated during this process. The test measures the levels of one particular TREC, $\delta$Rec-$\psi$J$\alpha$, which is produced from approximately 70% of cells that express the $\alpha/\beta$ T cell receptor. TRECs are absent or present in low numbers in newborns with SCID, as the underlying characteristic of all SCID conditions is the absence or extremely low concentration of autologous or functional T cells. Importantly, TRECs are not produced by maternally engrafted T cells.[11-13] The TREC assay uses real time quantitative polymerase chain reaction (RT-qPCR) on DNA extracted from a dried blood spot (DBS) on a Guthrie card to quantify the number of TRECs. [11-13] DBS on Guthrie cards are currently used by newborn screening programs.

**Studies assessing the TREC assay as a newborn screening test for SCID**

Studies assessing the TREC assay as a newborn screening test for SCID are summarised in Table 7.

*Singleplex assay*

A single tier TREC assay for population-based newborn screening for SCID was first evaluated by Chan and Puck (2005),[14] and this study was included in the 2010 systematic evidence review.[1] In this study, TRECs were amplified using quantitative PCR from 23 children with SCID, two children with non-SCID immunodeficiencies, and 242 anonymised newborn screening cards (assumedly from children without SCID). The parallel amplification (separate reaction) of $\beta$-actin served as a control, indicating whether the specimen was satisfactory for analysis. The children with SCID had undetectable TREC levels. There were seven anonymised newborn screening cards where $\beta$-actin could be amplified but TRECs could not (false positives). The authors calculated a false positive rate of 1.5% among children in routine nurseries and 5% from children discharged from special care units. In the full evidence review prepared for the Secretary's

Advisory Committee on Heritable Disorders in Newborns and Children, Lipstein et al. (2009) used the results of this study to calculate the sensitivity and specificity of the test.[4] The test had sensitivity of 84% and specificity of 97.1% when the cut-off for the assay was undetectable TRECs, and a sensitivity of 100% and specificity of 97% for a cut-off of <30TREC.[4] Chan and Puck (2005) amplified TRECs from two 3mm punches from a DBS, which is equivalent to approximately 6μL blood. Therefore the cut-off quoted corresponds to <5TREC/μL.

Several publications published since October 2008 were identified in the search. Many of these publications centred on the pilot study of newborn screening in Wisconsin.[12,13,15,16] In Wisconsin, the following screening algorithm was used: TREC levels were measured from a 3.2mm punch from a Guthrie card; samples with a TREC value of less than 25/μL were repeated, and β-actin was amplified in parallel, on new punches from the Guthrie card.[13] If the TREC result remained less than 25/μL and the β-actin level was low, an inconclusive report was issued and a new newborn screening card was requested. If the TREC level remained at less than 25/μL and the β-actin level was normal, an abnormal report was issued and the primary care physician contacted. Flow cytometry or a repeat TREC assay on a new Guthrie card was then performed. Infants who had low numbers of naïve T cells by flow cytometry were referred to a clinical immunologist. Premature infants with inconclusive/abnormal results had their TREC levels monitored until the equivalent of 37 weeks' gestation. If the assay results were still abnormal, full-term criteria applied and the infant was referred for flow cytometry.[13] Cut-off for the assay was increased to 40/μL whole blood in August 2009.[16]

Baker et al. (2009) described the development of test in Wisconsin.[12] A similar approach was taken to the approach in Chan and Puck (2005), with β-actin amplified in parallel as a control.[12,14] The test was assayed on samples from one infant with SCID, whole blood depleted of naïve T cells (from one adult) and 5,766 deidentified DBSs (assumed to be from children without SCID). No TRECS were detected in either the SCID or the naïve T cell depleted samples, although β-actin was amplified normally. There was only one false positive from the 5,766 deidentified DBS when a cut-off of 25TREC/μL was used (β-actin amplified but TREC levels below cut-off). It should be noted that this is an assumed false positive as there was no follow-up. Routes et al. (2009) describes results of the pilot screening trial from January-December 2008.[13] Verbsky et al. (2012) is the most recent publication on screening in Wisconsin, and summarises screening results from 2008 to 2011.[16] During this time, 207,696 infants were screened. Seventy-two infants had an abnormal TREC assay. T cell numbers (analysed by flow cytometry) were normal in 38 infants, abnormal in 33 infants, and not performed in one infant. The authors calculate the positive predictive value of the TREC assay for T cell lymphopenia of any cause as 45.83% (32 infants with abnormal flow cytometry [true positives]/72 infants with an abnormal TREC assay [screen positives]), and specificity as 99.98%. Five infants with SCID/severe T cell lymphopenia requiring HSCT or other therapy were detected. We calculate the positive predictive value of the TREC assay for SCID or severe T cell lymphopenia as 6.9% (five infants with SCID or severe T cell lymphopenia [true positives]/72 infants with an abnormal TREC assay [screen positives]). A complementary retrospective chart review analysed the cause of death in 39 infants with an abnormal or inconclusive newborn screening test for SCID during the first two years of newborn screening in Wisconsin, who died prior to the assessment of immune function.[17] The majority of these infants (36/39) were premature (37 weeks gestation or less, 33/39 born before 33 weeks estimated gestational age). There was no evidence that SCID contributed to the death of any of these infants.

Results of screening in Wisconsin have also been presented at the 2011 Association of Public Health (APHL)Webcast Series on Newborn Screening for SCID.[18] Results from January 2008 to April 2011 were reported. [15] These results were also included in the Secretary's Advisory Committee on Heritable disorders in Newborns and Children report on the on the status of newborn screening for SCID (see Table 8).[10] Up until April 2011, 243,707 infants had been screened. TREC screening had been positive/flow cytometry had been requested for 50-53 infants (Baker [2011] states 53,[15] the Advisory Committee Report states 50.[10] N.B. This is in conflict with Verbsky et al. [2012] which states that 72 infants, of the 207,696 screened at that time, had a positive/abnormal TREC result[16]). Four infants were diagnosed with SCID.[10,15] Seven[10] or eight[15] were diagnosed with non-SCID T cell lymphopenia. Using the results from Baker (2011) we calculate that the TREC assay has a positive predictive value of 7.5% for SCID (four infants with SCID [true positives]/53 screen positives) and 22.6% for T cell lymphopenia (12 infants with T cell lymphopenia [true positives]/53 screen positives).[15]

A pilot of screening in California has also been performed. California used a testing algorithm similar to that used in Wisconsin, and the screening algorithm used and the results of the pilot were also presented as part of the 2011 APHL Webcast Series, as well as being included in the Secretary's Advisory Committee on Heritable disorders in Newborns and Children report.[10,18] The screening algorithm used is as follows: TRECs were amplified from a punch from a Guthrie card; if TREC levels were below a cut-off of 40/3μL, the assay was repeated, with β-actin amplification in parallel.[19] A positive result was recorded if there were fewer than 5 TREC/3μL and actin >5000/3μL or if TREC levels between 6-25/3μL and actin >10,000/3μL (although if the infant was in neonatal intensive care a repeat DBS was requested). If β-actin levels were low a repeat DBS was requested (N.B. It had been reported elsewhere that the cut-off used in California is 40/μL rather than 40/3μL[11]). According to the presentation, 370,000 infants have been screened, and 43 have had an positive/abnormal result and been referred for flow cytometry.[19] Fourteen cases of T cell lymphopenia have been identified, including five cases of SCID. We calculate that the TREC assay has a positive predictive value of 11.6% for SCID (five true positives/43 screen positives) and 32.6% for T cell lymphopenia (14 infants with T cell lymphopenia [true positives]/43 screen positives). (N.B. The values in the Secretary's Advisory Committee on Heritable disorders in Newborns and Children report [see Table 8] are again slightly different, even allowing for the fact that the results presented in the webcast series may extend beyond April 2011).

Another publication using a similar approach was identified. Morinishi et al (2009) used RT-qPCR to amplify TRECs in 471 healthy controls samples and samples from 18 patients with SCID in Japan.[20] TRECs were amplified from peripheral blood and DBS. In this study, RNase P was amplified in parallel as a control. TRECs were detectable in all control samples, and were below detection levels or significantly lower than controls in patients with SCID. They also report that the TREC assay costs $5 per sample.

*Multiplexed assay*

Massachusetts developed a multiplexed screening assay for newborn screening for SCID.[21] RNase P is amplified in the same reaction as TRECs as an internal control. In Gerstel-Thompson et al. (2011) the assay was tested on 25,609 samples from population based controls and 8 infants with SCID.[21] SCID infants had TREC values below the cut-off value of 252/μL whole blood, with majority of SCID infants with undetectable TRECs. Preliminary results that demonstrate the capacity for the eluate and the residual ghost from a DBS to be used for multiplexed immunoassays and DNA tests were also reported.

Comeau et al. (2010) describe the screening follow-up algorithm and the preliminary results of one year of screening in Massachusetts.[22] Samples with TREC values less than twice the minimum standardized value on the calibration curve were re-tested in duplicate with new 3mm punches from the same specimen. If two or three samples had TREC values below the cut-off, and RNase P above cut-off, the specimen was considered positive for SCID. These infants would have flow cytometry. Specimens without amplifiable DNA (RNase P values below cut-off on 2 of the 3 results) were considered unsatisfactory, and a new sample requested. Unlike in Wisconsin, infants in special care units were referred for flow cytometry/further functional testing if TREC values were below cut-off, in a similar manner to full-term infants. However, they state that in some infants this second tier assessment cannot be performed. In these cases, they recommend that the infants have an immunology consultation and that TREC levels are monitored, with functional testing performed as soon as possible.[22] In a presentation at the APHL Newborn screening and genetics webcast series, the current referral algorithm used in Massachusetts was presented.[23] The cut-off vales (per µL whole blood) were 4,032 for RNase P, and 504 for TREC on the first assay. If either or both values were below cut-off, duplicates of the same specimen were retested. On repeat samples, the cut-off was 4032 for RNase P and 252 for TREC. This algorithm has been slightly modified: patients with undetectable TREC on the initial assay are referred for immediate flow cytometry; a request for a repeat DBS is made for patients with TREC levels lower than 252/µL; and a patient with serial samples with TREC levels lower than 252/µL is referred for flow cytometry. If any specimen from the same infant has in-range TREC, no flow cytometry is performed.

In the first year of screening, 68,811 infants were screened.[22] Fifty-one infants had a positive screen and were referred for flow cytometry, with 19 of these infants having results indicating T cell lymphopenia. No cases of SCID were identified. We also extracted the results presented in the APHL Newborn screening and genetics webcast series. This gave details of the screening program from February 2009 to May 2011.[23] This gave results not consistent with those published in Comeau (2010)[22], stating that of 161,707 infants screened only 28 infants were referred for flow cytometry, and of these 15 cases of T cell lymphopenia were identified, including one case of SCID.[23] These results are consistent with values in the Secretary's Advisory Committee on Heritable disorders in Newborns and Children report (see Table 8). Using the results in the Webcast series, we calculate that the TREC assay has a positive predictive value of 3.6% for SCID (one infant with SCID [true positive]/28 screen positives) and 53.6% for T cell lymphopenia (15 cases of T cell lymphopenia [true positives]/28 screen positives).

New York is reported to also perform a multiplexed TREC assay, and the results were also presented as part of the APHL 2011 Webcast Series.[11,18] However, slides from this presentation were not available.

| Author | Population | Significant Findings |
|---|---|---|
| Baker (2009)[12] | 5,766 deidentified DBSs (population based controls)<br>1 infant with SCID and whole blood depleted of naïve T cells | -Used RT-qPCR to quantify TRECs. β-actin was amplified in parallel<br>-The mean and median numbers of TRECs from 5,766 deidentified DBSs were 827 and 708, respectively, per 3.2mm punch (approximately 3µL whole blood)<br>-TREC levels in 61 control samples were below the cut-off after initial analysis. PCR on these samples was repeated. After repetition, only one sample was below the cut-off (TRECs could not be amplified, although β-actin amplified normally)<br>-No TRECs were detected in either the SCID or naïve T cell depleted samples, although β-actin was amplified normally |
| Baker (2011)[15]†‡ | 243,707 infants. Wisconsin January 2008-April 2011 | -243,707 infants screened<br>-Flow cytometry requested for 53 infants<br>-12 confirmed cases of T cell lymphopenia (4 SCID, 8 non-SCID T cell lymphopenia)<br>-Additional 17 cases with abnormal flow cytometry results. It was not reported whether these cases has clinically significant treatable conditions |
| Comeau (2010)[22]* | 68,811 infants. Massachusetts February 2009-January 2010 | -Used multiplexed RT-qPCR to amplify RNase P (internal control to monitor DNA quality and amount) and TRECs at the same time<br>-51 infants had a positive result and met criteria for flow cytometry; 49 of the 51 were from neonatal intensive care units<br>-19 (37%) had flow cytometry results indicating T cell lymphopenia<br>-no cases of SCID identified |
| Comeau (2011)[23]*‡ | 161,707 infants. Massachusetts (February | -161,707 infants screened<br>-28 infants had flow cytometry (19 infants in neonatal intensive care units, 9 |

| Author | Population | Significant Findings |
|---|---|---|
| | 2009- May 2011) | not in neonatal intensive care units)<br>-15 cases of T cell lymphopenia identified (1 case of SCID, 14 cases of non-SCID T cell lymphopenia) |
| Gerstel-Thompson (2010)[21] | 25,609 population based controls<br>8 infants with SCID | -Used multiplexed RT-qPCR to amplify RNase P and TRECs at the same time<br>-SCID infants had TREC values below the cut-off value of 252/µL whole blood, majority of infants did not have detectable TRECs<br>-The eluate and residual ghost from a DBS could be used as a source material for multiplexed immunoassays and multiplexes DNA tests |
| Lorey (2011)[19]‡ | 370,000 infants. California (August 2010- 2011 [month not reported, but presentation given in May 2011]) | -370,000 infants screened<br>-43 referred for flow cytometry (15 from regular nursery, 28 from neonatal intensive care)<br>-14 cases of T cell lymphopenia identified (5 cases of SCID, 6 SCID variants, 2 non-SCID T cell lymphopenia) |
| Morinishi (2009)[20] | 471 healthy controls (112 peripheral blood samples from volunteers [median age 14 years]; 33 umbilical cord blood samples, 26 Guthrie cards, 300 previously frozen Guthrie cards)<br>18 patients with SCID (peripheral blood before HSCT and stored Guthrie cards) | -Used RT-qPCR to amplify TRECs. RNase P amplified in parallel as an internal control<br>-TRECs were detectable in all control samples from whole blood and DBS (Guthrie cards)<br>-TRECs were below detection levels in most patients with SCID, or were significantly lower than controls ($10^1$ to $10^2$ copies/µg DNA) in both DBS and peripheral blood samples<br>-No false-positive or negative results in this study<br>-Report that the test costs $5 per sample |
| Routes (2009)[13]† | 71,000 infants (64,397 full-term and 6,603 pre-term). | -17 infants aged at least 37 weeks' gestation (or equivalent of 37 weeks gestation) had an abnormal TREC assay (<25/µL) |

| Author | Population | Significant Findings |
|---|---|---|
| | Wisconsin, January-December 2008 | -23 premature infants had an abnormal TREC assay initially, but only 3 infants had an abnormal TREC assay at the equivalent of 37 weeks gestation and went onto flow cytometry<br><br>-11 had samples analysed by flow cytometry to enumerate T cells (4 infants had a repeat TREC assay on a new Guthrie card that yielded a normal result, 1 infant died of causes unrelated to immunodeficiency and 1 infant not tested at parents' request)<br><br>-8 infants demonstrated T cell lymphopenia<br><br>-The causes of T cell lymphopenia included DiGeorge syndrome (n=2), idiopathic T cell lymphopenia (n=2), extravascular extravasation of lymphocytes (n=3) and *Rac2* mutation (n=1)<br><br>-No cases of SCID identified |
| Verbsky (2012)[16]† | 207,696 infants (188,741 full-term infants and 18,955 pre-term infants). Wisconsin, 2008-2011 | -72 infants had an abnormal assay<br><br>-The repeat testing rate in pre-term infants (infants with an abnormal or inconclusive result) was 0.16%<br><br>-T cell numbers (analysed by flow cytometry) were normal in 38 infants, abnormal in 33 infants, and not performed in one infant<br><br>-Positive predictive value of the TREC assay for T cell lymphopenia of any cause is 45.83%, specificity of 99.98%<br><br>-5 infants with SCID/severe T cell lymphopenia requiring HSCT or other therapy were detected (7% of infants with abnormal TREC assays) |

**Table 7: Studies of the TREC assay as a newborn screening test for SCID. *Overlap in populations included in these studies. †Overlap in populations included in these studies ‡Not published in peer-reviewed journals.**

Interim results of other the US SCID pilot studies (Louisiana, , New York, Puerto Rico, and the Navajo Nation in addition to Wisconsin, Massachusetts, California described above) were also collated for the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children report on the status of newborn screening.[10] It is reported that Wisconsin, California and Pennsylvania all perform a singleplex assay. A control gene (β-actin) is amplified concurrently with the TREC but only after an inconclusive or abnormal initial result is reported.[11] Massachusetts, Texas and New York all perform a multiplexed TREC assay, where RNase P is simultaneously amplified.[11] Up to March 2011, 961,925 newborns had been screened. A total of 364 newborns had a positive screen and required further testing. The numbers are shown by state in Table 8. Sixty infants had been diagnosed with some form of T cell immunodeficiency and 14 infants had been diagnosed with SCID (Table 8). There have been no reported cases of SCID that have been missed by screening. Using the results presented in the Secretary's Advisory Committee report, and assuming no missed cases of SCID (all test negatives are true negatives) we can calculate that for SCID the TREC test has:

- A sensitivity of 100% (indicating that all known cases of SCID were identified)
- A specificity of 99.96%
- A positive predictive value of 3.85% (14 infants with SCID [true positives]/364 screen positives)
- A negative predictive value of 100%

If all cases of T cell lymphopenia are included (including SCID and SCID variants), the positive predictive value of the TREC assay increases to 16.5% (60 cases of T cell lymphopenia [true positives]/364 screen positives). It is not possible to calculate the sensitivity, specificity or negative predictive value for T cell lymphopenia because it is unknown whether all cases of T cell lymphopenia were identified. It should be stressed that these values have been calculated assuming that no cases of SCID have been missed. As other reports have stated that it is difficult to determine the prevalence and incidence of SCID because of deaths before diagnosis, this may not be a valid assumption.[1]

It should also be noted that the screen positives are the screen positives reported by each state participating in the screening pilot. As mentioned above, the different states used either a singleplex assay or a multiplex assay, and the cut-off values for a positive result varied (see Criterion 6). It should be also noted that the different states have different policies on screening in premature infants.[11] An increased level of false-positive results are seen in premature infants.[11] In the original paper describing the TREC assay Chan and Puck calculated a false positive rate for the TREC assay with a cut-off of undetectable TRECs of 1.5% among children in routine nurseries and 5% from children discharged from special care units (assuming that all deidentified newborn screening cards were from unaffected infants).[14] In Wisconsin, premature infants with inconclusive or abnormal results undergo repeat testing until a normal result or the equivalent of 37 weeks gestation is reached.[13] If the infant has an abnormal result at the equivalent of 37 weeks gestation, flow cytometry is performed. The repeat re-testing rate for pre-term infants between 2008 and the end of 2010 was 0.16%.[16] Up until the end of April 2011, flow cytometry was requested for 53 infants, three of whom were premature, from the 243,707 infants screened. Twelve infants (of all infants screened) had T-cell lymphopenia, including four cases of SCID.[16] In California, cut-offs vary slightly for infants in neonatal intensive care compared to infants in normal nurseries, but infants with abnormal screens are referred for flow cytometry immediately.[19] This has resulted in 44 infants being referred for flow cytometry, with

28 infants from neonatal intensive care, from the 370,000 infants screened. Fourteen confirmed cases of T-cell lymphopenia have been identified, including five cases of SCID. Lorey concluded that "we are probably still doing too many unnecessary flows on NICU kids."[19] In Massachusetts screening uses a multiplex assay. All infants with abnormal results have been referred for flow cytometry. Until the end of April 2011, a total of 161,707 infants have been screened. Twenty eight infants have been referred for flow cytometry, 19 from neonatal intensive care, and 15 cases of T cell lymphopenia have been identified, from all infants screened, including one case of SCID.[23]

| State | Start of Screening | Number of Months Screening | Annual Births or Number Studied | Number of Infants Screened as of April 30, 2011 | Number of Negatives (TREC copy number above cut-off) | Number of Positives (TREC copy number below cut-off) | SCID | SCID Variant | Non SCID |
|---|---|---|---|---|---|---|---|---|---|
| Wisconsin | 1/1/2008 | 40 | 69,232 | 243,707 | 243,657 | 50 | 4 | 0 | 7 |
| Massachusetts | 1/2/2009 | 27 | 77,022 | 161,707 | 161,679 | 28 | 1 | 0 | 14 |
| Navajo Nation | 1/2/2009 | 27 | 2,000 | 1,297 | 1,296 | 1 | 0 | 0 | 0 |
| New York | 30/9/2010 | 7 | 236,656 | 136,635 | 136,412 | 223 | 4 | 0 | 12 |
| California | 1/8/2010 | 9 | 510,000 | 358,000 | 357,954 | 46 | 5 | 6 | 3 |
| Puerto Rico | 1/8/2010 | 9 | 45,620 | 29,115 | 29,107 | 8 | 0* | 0 | 3 |
| Louisiana | 1/10/2010 | 7 | 65,268 | 31,464 | 31,456 | 8 | 0 | 0 | 1 |
| | Total | 126 | 1,005,798 | 961,925 | 961,561 | 364 | 14 | 6 | 40 |

**Table 8: Summary of screening pilots until April 30, 2011. * One infant with suspected SCID died before diagnosis. NB the screening protocol and cut-off values varied between states. Taken from the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children report on the status of newborn screening for SCID.[10]**

**Publications on other potential screening tests for SCID, performed on DBS on Guthrie cards**

The development of other screening tests for SCID is also progressing. Studies of screening tests for SCID performed on DBS on Guthrie cards are summarised in Table 9.

*Tandem mass spectrometry (TMS)*

A case-control study investigated the possibility of using TMS to determine levels of adenosine and 2'-deoxyadenosine in DBS as a screening test of a particular subtype of SCID, ADA-SCID.[24] ADA catalyses the deamination of adenosine and 2'-deoxyadenosine, and in ADA-SCID levels of these two metabolites are increased. In this study adenosine and 2-deoxyadenosine levels were measured in 12,020 controls (including premature infants) and four patients with ADA-SCID. Patients with ADA-SCID had high levels of adenosine (mean ± standard deviation 7.8±3.1 µmol/L, lower limit 4.4 µmol/L) and 2'-deoxyadenosine (8.5±6.0µmol/L, lower limit 2.5µmol/L), whereas 2'-deoxyadenosine was not detected in any of the 12,020 controls, and the upper limit for adenosine was 0.81µmol/L. Therefore, patients with ADA-SCID could be easily distinguished from controls, as there was no overlap in values. This approach has the advantage of using technology (TMS) that is already used for newborn screening, for example to screen for medium chain acyl-CoA dehydrogenase deficiency.[25] The authors estimate the cost per test as €0.01 ($0.013).[24] However, only ADA-SCID can be screened for. The authors report that a trial of population-based screening for ADA-SCID using TMS started in September 2010 in Italy.[24]

*Immunoassays*

CD3 is part of the T cell receptor complex on mature T cells. An immunoassay against CD3 using DBS has been developed. Janik et al. (2010) performed a population study to determine a range for CD3 and CD45 levels (CD45 was used as an internal control).[26] A validation study on 8 coded punches from the New England Newborn Screening Program was then performed. All infants were correctly identified.[26] In another study, the immunoassay was further validated on 124 coded neonatal dry blood spots obtained from the Danish Newborn Screening Biobank.[27] Again, all infants with SCID or T cell related immunodeficiencies were correctly identified.[27] The immunoassay was also able to identify infants with SCID who had maternal engraftment of T cells.[26,27]

*Reverse phase high performance liquid chromatography (HPLC)*

A test for ADA deficiency, by determining ADA activity in DBS using reverse-phase HPLC, is also being developed.[28]

**Summary: Criterion 5 Partly Met**

**The most intensively studied screening test for SCID is the TREC assay. It uses RT-qPCR to amplify TRECs from dried blood spots on Guthrie cards, which are already used for newborn screening. This test had been using in pilot newborn screening programs in the US, where it has demonstrated high sensitivity and specificity with no reported cases of SCID that have been missed by screening. However, the positive predictive value of the test is poor, identifying only 14 infants with SCID from 364 screen positives. This is partly due to the fact that SCID is a rare condition, but also because the test identifies children with other T-cell deficiencies or lymphopenias. False positive results are also often obtained from premature babies.**

| Author | Population | Significant Findings |
|---|---|---|
| Azzari (2011)[24] | 12,020 healthy newborns<br>4 patients with genetically confirmed ADA-SCID | - Used tandem mass spectrometry to screen for infants with ADA-SCID by analysing levels of adenosine and 2'-deoxyadenosine<br>-Patients with ADA-SCID had high levels of adenosine (mean ± standard deviation 7.8±3.1 µmol/L, lower limit 4.4 µmol/L) and 2'-deoxyadenosine ( 8.5±6.0µmol/L , lower limit 2.5µmol/L)<br>-2'-deoxyadenosine was not detected in any of the 12,020 controls, and the upper limit for adenosine was 0.81µmol/L (including premature infants).<br>-Estimate cost per test as €0.01 ($0.013)<br>-Pilot program started in Italy |
| Janik (2010)[26] | 3 control infants<br>4 patients with SCID | -Used a multiplexed immunoassay to detect CD3 (T cells) and CD45 (total leukocytes, internal control)<br>-All infants correctly identified<br>-CD3 levels in control and SCID infants were 10-fold different |
| Janik (2011)[27] | 113 control infants<br>11 patients with T cell related immunodeficiencies (9 with SCID) | -Improved CD3 immunoassay<br>-Samples from healthy infants had T cell counts ranging between $2.14x10^6$/mL to $>16x10^6$/mL.<br>-Infants with T cell related immunodeficiencies had lower estimated T cell counts than controls. These counts ranged from below the limit of detection to $1.07x10^6$/mL<br>-All infants correctly identified |

**Table 9: Studies assessing other potential screening tests for SCID, performed on DBS on Guthrie cards.**

## 6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

The range in TREC levels observed and the cut-offs for a positive/abnormal screen in studies that assessed the TREC assay for newborn screening, are shown in Figure 1, Figure 2, Figure 3 and Table 10. The cut-off values used in screening programs which were presented as part of the APHL Webcast series are shown in Table 11. Note that there is some duplication of information; for example, Routes et al. (2009)[13] and Verbsky et al. (2012)[16] both describe the Wisconsin screening pilot, and Comeau et al. (2010)[22] describes the Massachusetts screening pilot.

Wisconsin, California and Pennsylvania all perform a singleplex assay.[11] A control gene (β-actin) is amplified concurrently with the TREC (in a separate assay) but only after an inconclusive or abnormal initial result is reported. The range of TREC values in Wisconsin in the development of the screening test and in the first year of screening (2008) are shown in Figure 1 and Figure 2. Publications and presentations from Wisconsin and California reported that a cut-off between 13/ µL whole blood (California)[19] and 40/µL whole blood (Wisconsin, introduced after August 2009).[15,16] These cut-offs are calculated by assuming that every 3.2mm punch has 3µL blood. However, it has been reported that the cut-off in California and Pennsylvania is also 40/µL.[11]

The number of TREC/µL whole blood is much higher in publications from Massachusetts, where a multiplex assay is used. The range of TREC values seen in Massachusetts is shown in Figure 3. Gerstel-Thompson et al. (2010)[21] use 252/µL whole blood as a cut-off, and in the Massachusetts presentation 504/µL is quoted as the cut-off in the initial assay.[23] This is reportedly because Massachusetts defines the cut-off based on the direct comparison of the TREC amplification to RNase P amplification, resulting in a higher TREC cut-off.[11]

Although the range of TREC values seen and the cut-off used varies depending on the exact assay used, in the US the test has shown excellent analytical validity. The US Centres for Disease Control and Prevention provides DBS reference materials for within-laboratory quality control and between-laboratory proficiency testing. The Secretary's Report on Newborn screening report states that "the tests showed 100 percent sensitivity (how often the test results are positive when TRECs are present) and more than 99 percent specificity (how often the test results are negative when TRECs are not present) in discriminating abnormal from normal TREC content in the reference materials."[10]

No publications were identified which looked at TREC levels as a function of gestational age. Pre-term infants often had inconclusive/abnormal results, leading Wisconsin to monitor TREC levels until infants reach the equivalent of 37 weeks gestation before a positive screening result was issued and the infant referred for flow cytometry.[13] However, the policy on SCID newborn screening varies from state to state.[11]

No studies were identified which looked at the range or cut-off values in the UK population.

**Summary: Criterion 6 Partly Met**

**The distribution of TREC values in DBS in the population and cut-off values applied in the pilot studies in US states have been published. The use of different methodologies (singleplex versus multiplex PCR) affects the TREC cut-off. The distribution of TREC values in the UK population will have to be determined and the cut-off value for SCID validated if a TREC assay is chosen.**

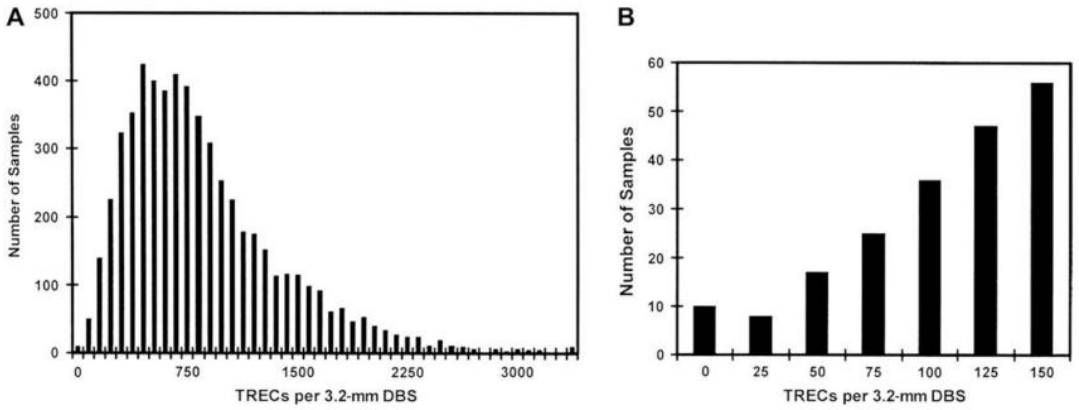



**Figure 1: The distribution of TREC values in DBS on 5,766 deidentified newborn screening cards (assumed to be from non-SCID infants) found during the development of a routine newborn screening protocol for SCID in Wisconsin. A singleplex RT-PCR assay was used. A: TREC copy number distribution, the mean is 827 and the median is 708 per 3.2mm DBS (equivalent to a mean of 275/μL blood and a median of 236/μL blood). B: The number of samples with a TREC copy number ≤150 per 3.2mm DBS. Sixty-one samples (1% of the total) have fewer than 75 TRECs per 3.2mm DBS (or 25 TRECs/μL). Figure taken from Baker et al. (2009).[12]**

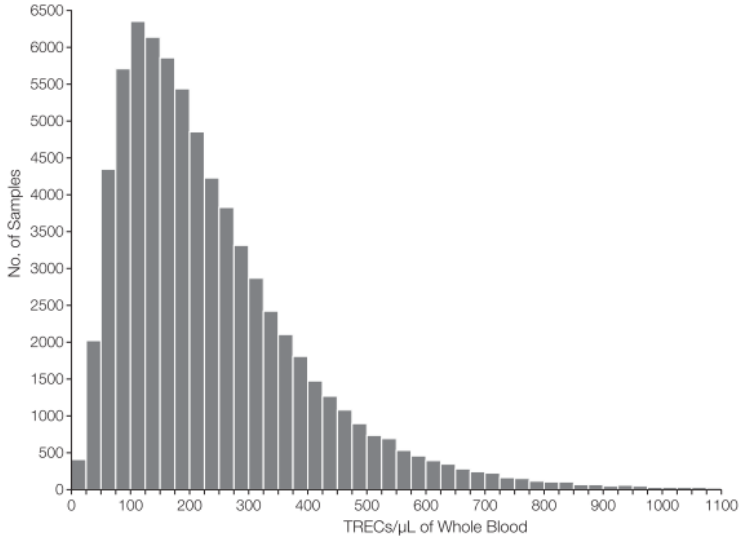



**Figure 2: The distribution of TRECs in DBS on newborn screening cards in Wisconsin in 2008 (71,000 infants). A singleplex RT-PCR assay was used. The mean number of TRECs was 225 TRECs/μL of whole blood and the median was 186 TRECS/μL of whole blood. A total of 115 samples have TRECs of more than 1050/μL. Figure taken from Routes et al. (2009).[13]**

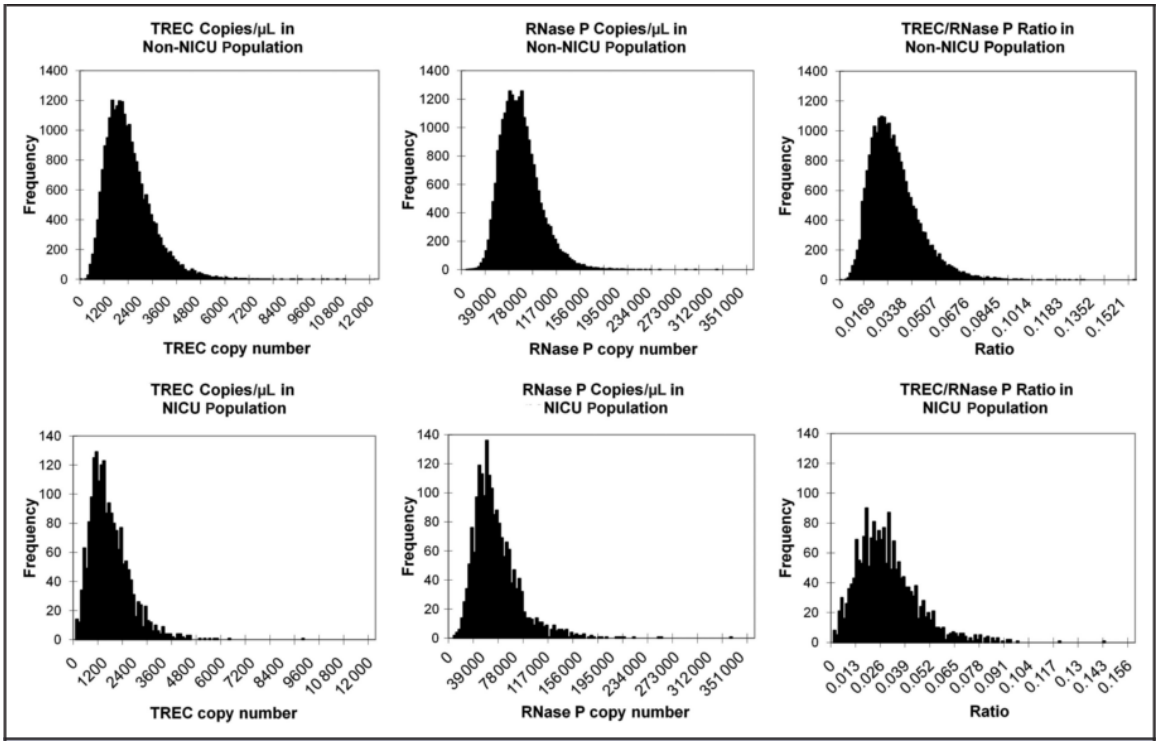



**Figure 3: The distribution of TREC and RNase P copy number among neonatal intensive care and non-neonatal intensive care populations in Massachusetts, using the multiplexed RT-PCR assay. Figure taken from Gerstel-Thompson et al. (2010)[21]**

| Author | Population | TREC levels | Control levels | TREC Cut-off |
|---|---|---|---|---|
| Baker (2009)[12] | 5,766 deidentified DBSs | TREC/3.2mm punch (approximately 3µL whole blood)<br>827 (mean)<br>708 (median) | β-actin, levels not reported | 75/3.2mm punch (approximately 3µL whole blood) |
| Comeau (2010)[22] | 68,811 infants. Massachusetts February 2009-January 2010 | Not reported | RNase P, levels not reported | TREC values less than twice the minimum standardized value on the calibration curve |
| Gerstel-Thompson (2010)[21] | 25,609 control infants<br>23,667 not in NICU<br>1,942 in NICU<br>8 SCID patients | TREC/µL whole blood, mean<br>$1.9 \times 10^3$<br>$2.0 \times 10^3$<br>$1.4 \times 10^3$<br>28.1* (maximum $1.4 \times 10^2$) | RNase P/µL whole blood, mean<br>$7.1 \times 10^4$<br>$7.2 \times 10^4$<br>$5.5 \times 10^4$<br>$3.3 \times 10^4$ | 252/µL whole blood |
| Morinishi (2009)[20] | 26 controls<br>15 SCID patients | TREC/µg DNA, mean<br>$2.3 \times 10^4$<br>41.3* (maximum $6.2 \times 10^2$) | RNase P/µg DNA, mean<br>$2.3 \times 10^6$<br>$1.8 \times 10^6$ | Not determined |
| Routes (2009)[13]† | 71,000 infants (64,397 full term and 6,603 premature). Wisconsin January-December 2008. | 225/µL whole blood (mean)<br>186/µL whole blood (median) | β-actin, only amplified during repeat PCR on samples with TREC levels below cut-off. β-actin levels not reported | 25/µL whole blood |
| Verbsky | 207,696 infants (188,741 full-term infants and 18,955 pre- | Not reported | β-actin, levels not reported | 25/µL whole blood. Cut-off was increased to 40/ |

| Author | Population | TREC levels | Control levels | TREC Cut-off |
|---|---|---|---|---|
| (2012)[16]† | term infants). Wisconsin 2008-2011 | | | µL whole blood in August 2009 |

**Table 10: Range of TREC values and cut-offs applied in studies of the TREC assay on DBS as a newborn screening test for SCID. *Calculated assuming that samples where TRECs were not detected had no TRECs. †Overlap in populations in these two studies. Abbreviations: NICU neonatal intensive care unit.**

| State | TREC cut-off | Control cut-off | Notes |
|---|---|---|---|
| California[19] | 40/punch (3µL whole blood) (initial assay)<br>5/3µL whole blood (repeat assay)<br>6 to 25/3µL whole blood (repeat assay) | β-actin<br>If TREC ≤5, 5000/3µL whole blood<br>If TREC 6-25, 10,000/3µL whole blood (if infant not in neonatal intensive care, otherwise repeat DBS requested) | - Pre-term infants/infants in neonatal intensive care units treated in the same way as term infants (except for β-actin cut-offs)<br>-β-actin amplified in a separate reaction if initial TREC assay less than 40/punch (3µL whole blood) |
| Massachusetts[23] | 504/µL whole blood (initial assay)<br>252/µL whole blood (repeat assay) | RNase P<br>4032/µL whole blood (initial and repeat screen) | -Pre-term infants/infants in neonatal intensive care units treated in the same way as term infants<br>-RNase P and TREC assay performed simultaneously<br>Modifications:<br>-Undetectable TREC on initial specimen→immediate flow cytometry<br>-TREC <252/µL on initial assay→request repeat DBS<br>-Serial TREC <252/µL →flow cytometry<br>-Any in-range TREC on a specimen→no flow |

| State | TREC cut-off | Control cut-off | Notes |
|---|---|---|---|
| | | | cytometry |
| Wisconsin[15] | 40/µL whole blood (initial assay) for term infants<br>25/µL whole blood (initial assay) for pre-term infants<br>25/µL whole blood (repeat assay) (for full-term and pre-term infants) | β-actin<br>10,000/µL whole blood (for full term and pre-term infants) | -β-actin amplified in a separate reaction if initial TREC assay below cut-off |

**Table 11: Cut-off values in pilot screening programs, as reported in presentations in the 2011 APHL Webcast Series.[18]**

## 7. The test should be acceptable to the population

The TREC test is performed on DBS on Guthrie cards, which are already collected as part of the newborn screening programme.[29]

**Summary: Criterion 7 Met**

**The TREC test is performed from the dried blood spot collected for the newborn screening programme.**

## 8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

In the full evidence review on SCID prepared for the Advisory Committee on Heritable Disorders in Newborns and Children Lipstein et al. state that "Review of the literature found no evidence that describes any specific diagnostic testing protocol for SCID. We suspect this reflects the time-frame used in the literature search and that diagnostic testing protocols were established prior to 1988. Articles that make reference to diagnostic testing and the experts with whom we spoke all utilize flow cytometry… testing T cell response to mitogens…additionally, several researchers (Vogt, Puck, Buckley, Notarangelo, Pai and Bonilla) commented on gene sequencing."[4]

No evidence for a specific diagnostic testing protocol for SCID was identified in the update search. However, several publications were identified which gave expert recommendations on the diagnostic protocol, and we also report the diagnostic protocol used for infants with a positive newborn screening test used by the states of Massachusetts and Wisconsin.

Expert guidance on the recognition, diagnosis and management of primary immune deficiency diseases including SCID has been published.[30] It recommends that the following tests are performed for the diagnosis of SCID:

- Flow cytometry using antibodies to CD3, CD4, CD8, CD19 and CD16/56 to determine whether the infant has normal percentages of T cells and subsets, B cells and NK cells
- Assessment of the proliferative response of T cells *in vitro* to mitogens (such as phytohaemagglutinin [PHA], concanavalin A, and pokeweed mitogen) and antigens (for example *Candida* species)
- Potential gene defects can be predicted from the immunophenotypic pattern. The gene defect can be confirmed by sequencing. "DNA sequencing of specific SCID genes can enable the immunologist to better inform parents of the potential future outcomes of their child once treated…and to provide genetic counselling." Although a genetic diagnosis is not required for HSCT, knowledge of the mutation responsible for SCID can also inform treatment options. For example, myoablative conditioning may be avoided in patients with SCID due to mutations that results in defective DNA repair (for example Artemis and ligase IV deficiency).

van der Berg and Gennery (2011) have also listed diagnostic tests for SCID;[31] these include:

- Flow cytometric immunophenotyping of peripheral blood. Flow cytometry can also be used to determine the clonality of any T cells present

- If maternal engraftment of T cells is suspected, this can be confirmed by HLA typing or determined by XY FISH if the infant is male
- Protein expression of candidate genes
- Flow cytometric analysis of B cell compartment in the bone marrow
- Sequence analysis of candidate genes
- Other functional tests: *in vitro* function tests to determine enzymatic activity; analysis of the sensitivity of fibroblasts to ionizing radiation; analysis of the coding joints of immunoglobulin gene rearrangements in bone marrow precursor B cells, *in vivo* V(D)J recombination studies. These tests are not routinely performed in a diagnostic setting

In the Massachusetts screening program a positive SCID newborn screening result was followed by a two-tiered diagnosis evaluation: flow cytometry on blood samples to measure levels of specific T cell markers and markers of B cells and NK cells, followed by clinical diagnostic evaluation including a physical exam and specialised immune function tests.[22] Flow cytometry measured the number of cells expressing CD3, CD4, CD8, CD16/56, CD19 and determined the number of naïve T cells.[23] Infants were referred for a clinical exam if they had fewer than 2,500 T cells, less that 50% naïve T cells or if they had any other abnormality.[23]

In Wisconsin, infants with positive screening results also had lymphocyte subset analysis by flow cytometry.[16] The number of cells expressing CD3, CD4, CD8, CD19, CD45, CD45RO and CD56 was measured. Infants with abnormal flow cytometry were referred for evaluation by a clinical immunologist.

Publications relating to SCID mutation diagnosis were also identified. For example, a custom re-sequencing microarray has been investigated.[32] It contained probes representing exons and flanking regions of known SCID genes. As mentioned above, mutation identification is not a prerequisite for diagnosis or treatment, but can aid diagnosis, treatment decisions, and give an indication of prognosis.

**Summary: Criterion 8 Met**

**Guidance on the clinical and laboratory assessments that should be performed if SCID is suspected; and the policy on diagnostic tests used on screening-positive infants in the US pilot studies has been published. The place of gene sequencing is unclear although flow cytometry and immune function testing is well described.**

## 9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

**Criterion 9 Not Applicable.**

## 10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

The Lipstein et al. (2010) systematic evidence review states that “the life-saving nature of treatment for SCID, especially HSCT, has been documented over many years…two other treatments, enzyme replacement therapy and gene therapy, have been studied in small trials of

children with specific SCID subtypes."[1] The review concentrated on two questions: whether earlier treatment (with HSCT) improves outcomes, and if variations in HSCT protocols, including the degree of donor-recipient matching and the use of pre-transplant myeloablation, improves outcomes.[1]

The review included four studies that had assessed the effect of early treatment of SCID (Table 12). It concluded that "children who receive early HSCT consistently do better than those who receive later treatment."[1]

| Author, Study Design | Population | Significant Findings |
|---|---|---|
| Antoine et al[26] (2003), case series | 475 patients with SCID: 202 were <6 mo old at transplant, 184 were between 6 and 11 mo old at transplant, and 89 were >3 mo old at transplant | After HLA-identical transplant, 3-y survival rate varied according to age at transplant: 92% for children <6 mo old, 50% for children 6–11 mo old, and 31% for children ≥12 mo old; children who received a transplant at <6 mo of age had better 3-y survival rates than those of the older cohorts; survival rates have improved over time for both HLA-identical and non–HLA-identical transplant recipients |
| Buckley et al[7] (1999), case series | 89 children total: 22 were <3.5 mo old at transplant, and 67 were ≥3.5 mo at transplant | Overall survival rates: 95% (21 of 22) among those who received a transplant before 3.5 mo, and 76% (51 of 67) among those who received a transplant after 3.5 mo; median follow-up: 5.6 y |
| Kane et al[27] (2001), case series | 13 children who received a transplant between 7 and 68 d of age | All patients were alive and well 0.5–11.5 y after transplant (median: 3 y); 3 children required >1 transplant; 10 of 12 had normal neurodevelopment; 1 of 12 had trouble with communication and interactive skills; and 1 of 12 had motor delay |
| Myers et al[25] (2002), cohort study | 117 children total: 21 children who received a transplant before 28 d of life (early treatment) and 96 children who received a transplant later (range: 45–516 d) (late treatment) | 20 of 21 (95%) children who received early treatment survived (8 mo to 19.2 y); 71 of 96 (74%) children who received late treatment survived; mean TREC value peaked earlier after transplant for early-treatment recipients, but the 2 groups were indistinguishable by 5 y; early transplantation did not have an effect on B-cell function |

**Table 12: Evidence related to early treatment of SCID. There is a potential overlap of patients included in the studies of Myers et al. 2002 and Buckley et al. 1999. From the 2010 systematic evidence review of newborn screening and treatment of SCID.[1]**

The review included 10 studies which looked at the effect of donor- recipient matching in HSCT (Table 13) and six studies on the effect of myeloablation before HSCT (Table 14). It concluded that "recipients from matched relating donors [have] the best survival rate…in addition, some evidence indicates that pre-transplant conditioning may affect later B-cell function." However "determining the best mix of matching and conditioning will require systematic research."[1]

| Author, Study Design | Population | Significant Findings |
|---|---|---|
| Antoine et al[26] (2003), case series | 475 patients with SCID: 202 were <6 mo old at transplant, 184 were between 6 and 11 mo old at transplant, and 89 were >3 mo old at transplant | 3-y survival rate with sustained engraftment was 77% for HLA-identical and 54% for non–HLA-identical transplants; survival rates improved over time for both HLA-identical and non–HLA-identical transplant recipients |
| Dalal et al[33] (2000), case series | 16 children total, 9 with SCID | All received matched unrelated transplants; neutrophil engraftment was achieved in all patients at a mean of 15.4 d; 12 of 16 patients survived for 6–101 mo (mean: 47.4 mo); 2 of 9 (22%) patients with SCID died from GVHD complications |
| Dal-Cortivo et al[34] (2004), case series | 40 children total, 32 with SCID | All received haploidentical transplants; 2 patients died within 1 mo of transplant; 24 of 38 achieved primary engraftment; the 1-y survival rate was 52.5% (21 of 40) |
| Fischer et al[28] (1990), case series | 183 patients total: 70 who had an HLA-identical donor transplant and 113 who had a non–HLA-identical donor transplant | Survival rate was significantly better for HLA-identical (76%; median follow-up: 73 mo) than for non–HLA-identical (50%; median follow-up: 41 mo) transplants; the SCID phenotype was not associated with difference in survival |
| Giri et al[35] (1994), case series | 11 children total, all of whom received a non–HLA-identical BMT | 9 patients engrafted (8 after first BMT, 1 after second BMT); 4 of 9 developed GVHD; 5 (46%) patients survived 6–78 mo (median: 14 mo) after a BMT |
| Grunebaum et al[31] (2006), cohort study | 94 children total: 13 RIDs, 41 MUDs, and 40 MMRDs | Median time to transplant was 1 mo for RID, 2 mo for MMRD, and 4 mo for MUD; highest survival rate was with RID (92.3%; median follow-up: 96 mo), followed by MUD (80.5%; median follow-up: 40 mo) and MMRD (52.5%; median follow-up: 24 mo); 0% of RIDs, 7.3% of MUDs, and 30% of MMRDs had graft failure; no respiratory complications in children who received an RID; respiratory complications occurred in 7.3% of MUD and 35% of MMRD recipients; GVHD was most common after MUD BMT (73.1%) or MMRD BMT (45%) |
| Mazzolari et al[29] (2007), case series | 58 children total: 12 matched sibling transplants, 33 mismatched related donor transplants, 3 phenotypically identical donor transplants, and 10 matched unrelated donor transplants | 42 of 58 (72.4%) survived at least 5 y (median follow-up: 132 mo); degree of matching did not affect T-cell reconstitution; autoimmune complications were observed in 4 patients with mismatched related donor and 1 with matched unrelated donor |
| Smogorzewska et al[32] (2000), cohort study | 48 children total: 11 children treated with histocompatible transplants from a sibling and 37 children treated with T-cell–depleted haploidentical parental bone marrow | 100% survival rate (follow-up: 3–13 y) in histocompatible group; 46% survival rate in haploidentical group; mean age at transplant of children who survived: 7.5 mo; mean age at transplant of children who died: 11.4 mo |
| van Leeuwen et al[30] (1994), case series | 31 patients total: 10 RIDs, 19 HLA-haploidentical related donor transplants, and 2 closely HLA-matched unrelated donor transplants | 6 of 10 (60%) who received an RID survived, 9 of 19 (47%) who received an HLA-haploidentical related transplant survived, and 0 of 2 (0%) who received an HLA-matched unrelated transplant survived; patients were followed for 1–22.9 y after transplant; major causes of death were graft and respiratory failure; all who died of respiratory failure had a lung infection before the transplant |
| Wijnaendts et al[36] (1989), case series | 33 children total: 18 HLA-identical transplants and 15 non–HLA-identical transplants | Development of immune function occurred faster in patients with HLA-identical transplants; after HLA-identical transplant, had normal T-cell function within 4 mo; after non–HLA-identical transplant, normal T-cell function not present until 7 mo |

BMT, bone marrow transplant; RID, related HLA-identical transplant; MUD, HLA-matched unrelated transplant; MMRD, HLA-mismatched related transplant.

**Table 13: Evidence related to the role of donor-recipient matching in HSCT for SCID. From the 2010 systematic evidence review of newborn screening and treatment of SCID.[1]**

| Author, Study Design | Population | Significant Findings |
|---|---|---|
| Antoine et al[26] (2003), case series | 475 patients with SCID: 202 were <6 mo old at transplant, 184 were between 6 and 11 mo old at transplant, and 89 were >3 mo old at transplant | 205 received no conditioning chemotherapy; myeloablation before non–HLA-identical transplant trended toward improving the survival rate among children with B- SCID; conditioning regimen had no significant effect on the rate of sustained engraftment |
| Amrolia et al[39] (2000), case series | 8 patients total, 5 with SCID | All treated with nonmyeloablative chemotherapy before transplant; 7 of 8 children survived; at median follow-up of 12 mo, all 7 survivors had good recovery of T-cell numbers, 4 patients had normal IgM levels, and 2 patients had normal IgA levels |
| Buckley et al[7] (1999), case series | 89 children total: 22 were <3.5 mo old at transplant, and 67 were ≥3.5 mo at transplant | No children received chemotherapy; 72 (81%) were alive 3 mo to 16.5 y after their transplant, with a median follow up of 5.6 y; 65 survived for >1 y, 38 for >5 y, and 21 for >10 y; poor B-cell function (45 children required IVIg) |
| Friedrich et al[6] (2007), cohort study | 31 children total: 6 children with SCID who received an HLA-identical transplant and 25 children with SCID who received an HLA-haploidentical transplant | 13 of 25 children who received haploidentical transplants were pretreated with chemotherapy; children who received an HLA-haploidentical transplant with no conditioning had lower levels of naive $CD4^+$ cells and impaired B-cell functioning |
| Rao et al[38] (2005), cohort study | 52 children with primary immunodeficiency: 33 children received reduced-intensity pretransplant chemotherapy and 19 received myeloablation | All children in both groups had primary engraftment; reduced-intensity group: 32 of 33 alive at 1 mo and 31 of 33 alive at 1 y; myeloablation group: 14 of 19 alive at 1 mo and 11 of 19 alive at 1 y; at 1 y: all in the myeloablative group had normal B-cell function, 5 in the reduced-intensity group still required IVIg; GVHD incidence was not different between groups, but limited chronic GVHD was more common in myeloablation group; quality of life, measured by Lansky score, was similar between the groups (97 vs 94) |
| Veys et al[40] (2005), case series | 81 children total, 20 with SCID | All subjects were treated with HSCT with reduced-intensity conditioning; survival rate was 84% (68 of 81), and there was no significant difference on the basis of donor type or SCID vs non-SCID |

Ig, immunoglobulin; IVIg, intravenous immunoglobulin.

**Table 14: Evidence related to the role of myeloablation before HSCT for SCID. From the 2010 systematic evidence review of newborn screening and treatment of SCID.[1]**

The full review prepared for the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children also addressed:[4]

- Efficacy of HSCT
- HSCT efficacy in different genotypes and phenotypes of SCID
- The effect of other variations in HSCT
- Survival and immune reconstitution after HSCT in long term follow-up
- Outcomes in children treated with enzyme replacement therapy (PEG-ADA) for ADA-SCID
- Outcomes in children treated with gene therapy for ADA-SCID or X-linked SCID

In this review, we have concentrated on current guidance on SCID treatment, and the evidence regarding outcomes after early versus late treatment, survival after HSCT, and outcomes after gene therapy.

**Guidance**

Expert guidance on the recognition, diagnosis and management of primary immune deficiency diseases including SCID has been published.[30] It presents expert guidance on the medical management of infants who are suspected to have SCID/combined immunodeficiency disease (CID); primary immunodeficiency diseases that are indications for HSCT; and post-transplantation care.[30] The UK Primary Immunodeficiency Network also has a standard of care guideline for SCID.[33] The European Group for Blood and Marrow Transplantation and European Society for Immunodeficiencies (ESID) have produced guidelines for HSCT for primary immunodeficiencies, including SCID.[34]

**Pre-transplantation**

Pre-transplantation guidance is given in Griffiths et al. (2009) and in the care guideline from the UK Primary Immunodeficiency Network.[30,33] Main points are listed below and in Table 15.

- Refer infant to a transplantation centre (Great Ormond Street Hospital or Newcastle general Hospital in the UK)
- Place the infant in protective isolation
- Give prophylaxis against Pneumocystis pneumonia (PCP) and bacterial infections, other fungal and viral prophylaxis should also be considered
- Start replacement immunoglobulin
- Avoid breast-feeding pending determination of the mother's CMV serologic status
- Avoid vaccinations. The vaccination of siblings with varicella should also be avoided
- Identify and treat any infections. Infants who have received BCG vaccination must be commenced on isoniazid and rifampicin (or other suitable drugs)
- All blood products (platelets and erythrocytes) should be CMV seronegative, leukodepleted, or both to prevent transmission of CMV and irradiated to eliminate the risk of transfusion-associated graft-versus-host disease (GvHD)
- General:
    - Monitor height, weight and head circumference on a regular basis
    - Pay attention to skin care (in particular the nappy area in babies with diarrhoea) is crucial
    - Ensure adequate nutrition is given

| Management | Details |
|---|---|
| Refer to transplantation center as soon as possible. | 1. Protect against ill contacts. |
| | 2. Place in protective isolation with mandatory good hand washing to minimize exposure to hospital-acquired infections. |
| | 3. Manage as outpatient if clinically indicated. |
| | 4. A high degree of suspicion for infection is important, because infections can be clinically relatively asymptomatic due to immunity which is defective, in this highly susceptible patient population. |
| | Notes: The additional use of gowns, gloves and masks varies from center to center, with more than half using all of these isolation approaches with admittedly little to no documented proof of their efficacy. |
| Start PCP prophylaxis. | 1. Can start trimethoprim-sulfamethoxazole at 1 to 4 wk of age if total bilirubin level is not increased and monitor LFT results. |
| | 2. At 4-6 wk old, start trimethoprim-sulfamethoxazole or can use atovaquone, dapsone, or intravenous pentamidine (the latter is given every 2 wk). |
| | 3. At >6 wk old, trimethoprim-sulfamethoxazole is given orally 2-3 d/wk. |
| | Notes: Although trimethoprim-sulfamethoxazole is not recommended for children <6 wk of age because of possible hepatic toxicity, some experienced centers start it as early as 1 wk of age if the total bilirubin level is not increased and with careful monitoring of liver transaminase levels. The standard PCP prophylactic agent is trimethoprim-sulfamethoxazole administered orally 2-3 d/wk. Alternative therapies are available if trimethoprine-sulfamethoxazole cannot be given. |
| Consider fungal prophylaxis, especially for *Candida* species. | 1. Diflucan (fluconazole) |
| | 2. Monitor LFTs. |
| | 3. If liver inflammation is present, caspofungin is an alternative. |
| | Notes: Fluconazole should be considered to prevent primarily *Candida* species infection, again with careful monitoring of LFT results. |
| Start bacterial prophylaxis. | 1. IVIG: monitor IgG trough level and maintain >500-800; or fixed dose of 400-500 mg/kg per dose every 3 to 4 wks. |
| | 2. Subcutaneous gamma globulin is an option. |
| Consider viral prophylaxis. | 1. Acyclovir |
| | 2. Maintain adequate hydration. |
| | Notes: In terms of viral prophylaxis, there appears to be no consensus among immunologists/transplantation centers, with about half starting acyclovir at the time of diagnosis. |
| Breast-feeding | 1. Not an issue in terms of GVHD risk |
| | 2. Stop nursing until CMV status of mother is known; if seronegative, then it is okay to breast-feed. |
| | Notes: The likelihood of transmission of CMV to babies with SCID from breast milk is sufficiently significant that many immunologists/transplantation centers recommend stopping breast-feeding until the mother's CMV serologic status can be determined; if negative, then breast-feeding can be resumed. Development of GVHD from maternal lymphocytes known to be present in breast milk does not appear to be the case in human subjects. There are no documented cases of maternal-infant GVHD in babies with SCID as a result of breast milk, although it is obviously difficult, if not impossible, to differentiate from maternal-fetal GVHD, a known presenting feature of SCID. |
| Immunizations | 1. Avoid live vaccines, including rotavirus, MMR, Flu-mist, and BCG. |
| | 2. Siblings should NOT get varicella vaccine. |
| | Notes: Unfortunately, the early application of the live attenuated rotavirus vaccine has resulted in symptomatic infections in patients given subsequent diagnoses of SCID (personal communication, M. Cowan). Vaccination of healthy siblings with the varicella vaccine should be avoided. |
| Blood products | 1. Red blood cells and platelets should be CMV negative, if possible; leukodepleted; and irradiated. If CMV-negative blood is not available, then leukodepletion is essential. |
| | 2. Fresh frozen plasma does not require irradiation. |
| | Notes: A previous blood transfusion with nonirradiated blood has potential to transfer T lymphocytes capable of producing fatal transfusion-associated GVHD. |

**Table 15: Management of a child with suspicion for SCID/Combined immunodeficiency while confirming diagnosis. From Griffith et al. (2009).[30]**

## Treatment

Children with SCID can be treated with HSCT, which can be curative. Additional treatments for children with specific subtypes of SCID also exist: enzyme replacement therapy (ERT) for children with ADA-SCID; and gene therapy, which has been studied in small trials of children with ADA-SCID and X-linked SCID.

The European Group for Blood and Marrow Transplantation and ESID have produced guidelines for HSCT for primary immunodeficiencies.[34] These guidelines are updated annually, although they state that "the clinical heterogeneity of the patients, together with the fact that outcome data are based on observational studies, means that it is not yet possible to recommend tightly defined clinical protocols for transplanting these conditions. Each case needs to be carefully evaluated in a centre which has significant ongoing experience of performing these procedures. The exact transplant protocol will be devised using these guidelines, but sometimes modified according to the particular variant of the primary immunodeficiency and/or the patient's clinical condition." To treat SCID (defined as profound T cell lymphopenia or oligoclonal non-function T cells) they recommend that:

- No conditioning, T cell depletion or GvHD prophylaxis be used when the transplant is from a genotypically identical donor, although conditioning should be considered in

Omenn's syndrome with autoreactive T cells, SCID with maternal GvHD, and in those with failure of primary engraftment

- A secondary transplant should be considered if there is failure of T cell recovery one year after initial assessment
- With a matched unrelated donor (MUD), a phenotypically identical family donor, or umbilical cord blood (UCB), myeloablative conditioning is recommended (consisting of chemotherapy, serotherapy and GvHD prophylaxis). Peripheral blood stem cells are the preferred stem cell source for matched unrelated donors and matched family donors
- With a HLA-nonidentical donor, the use if a T cell depleted graft is recommended In conjunction with myeloablative conditioning
- In patients with T-B+ SCID under 3 months of age receiving transplantation from a haplo-identical donor, conditioning is not required, T cell depletion should be performed, and GvHD prophylaxis is not required

The guideline includes treatment algorithms for X-linked SCID and ADA-SCID, which include when ERT (for ADA-SCID) or gene therapy should be considered (see Figure 4 and Figure 5).

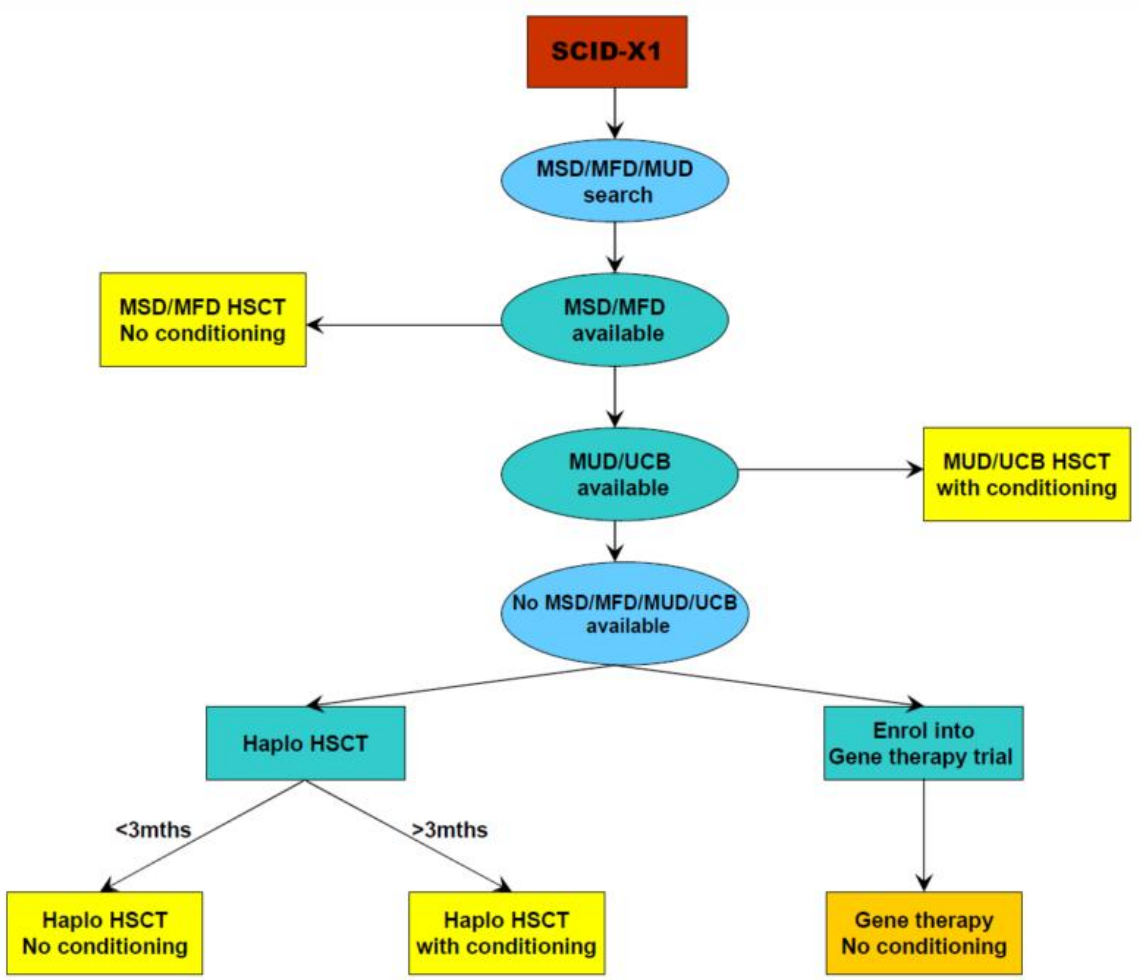



**Figure 4: Treatment algorithm for X-linked SCID. From the European Group for Blood and Marrow Transplantation and ESID guidelines for HSCT for primary immunodeficiencies.[34] Abbreviations: MSD, matched sibling donor; MFD, matched family donor; MUD, matched unrelated donor; UCB umbilical cord blood.**

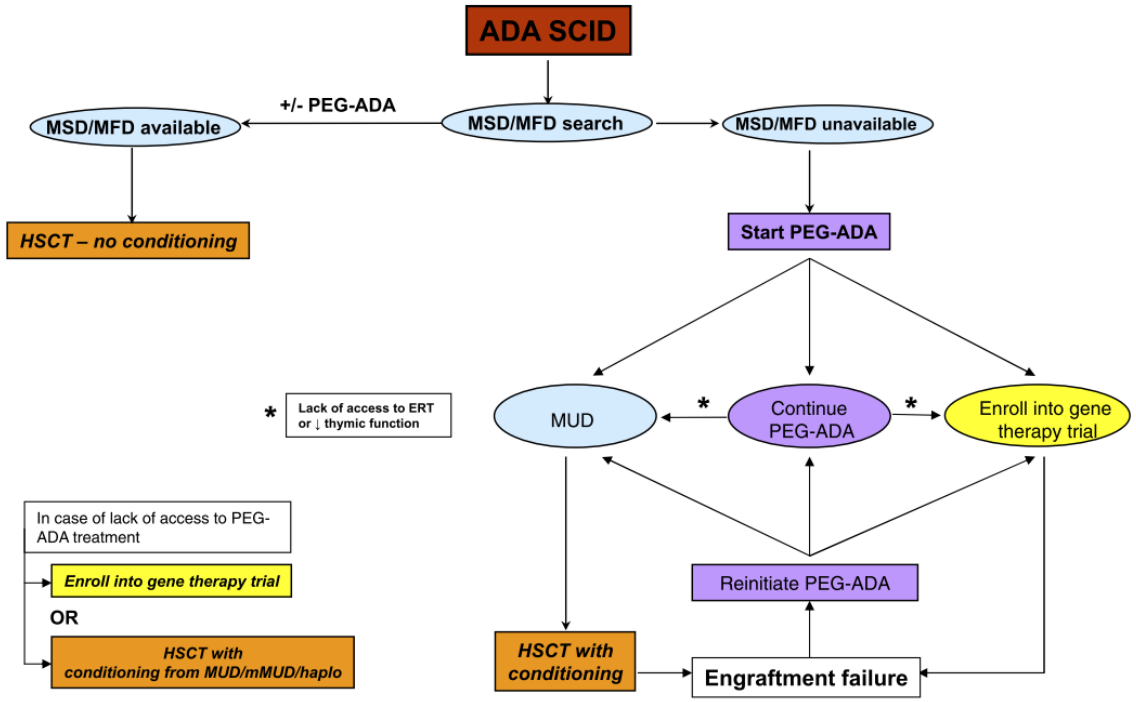



Figure 4. Flow chart for treatment of patients with ADA-SCID.

**Figure 5: Treatment algorithm for ADA-SCID. From the European Group for Blood and Marrow Transplantation and ESID guidelines for HSCT for primary immunodeficiencies.[34] Agreed by members of the Inborn Errors Working Party (IEWP) in conjunction with other experts.[35] Abbreviations: MSD, matched sibling donor; MFD, matched family donor; MUD, matched unrelated donor; mMUD, mismatched unrelated donor.**

### Post-transplantation

Griffith et al. (2009) also included management strategies for children with primary immunodeficiency diseases after HCT/other definitive treatment, which include:[30]

- Follow-up/monitoring
- Antimicrobial prophylaxis (length depends on time course of immune reconstitution and the patients pre- and post- HCT infectious disease history
- Gamma globulin supplementation

### Evidence related to outcomes after HSCT

We have concentrated on the evidence regarding outcomes after early versus late HSCT treatment and survival after HSCT.

*Early versus late diagnosis and treatment*

Five studies in which early versus late HSCT were compared were identified, summarised in Table 16. In all studies identified, treatment at a younger age was associated with improved survival.

Brown et al. (2011) compared survival in infants who were diagnosed early due to a family history of SCID with the first presenting family member, in children diagnosed between 1982 and 2010 and treated at Great Ormond Street Hospital or Newcastle General Hospital. Survival in first presenting members was 40%, whereas survival in the sibling cohort was 90%.[6] This study mainly analysed the benefits of early diagnosis, but concluded that "SCID babies diagnosed at birth have a significantly decreased number of infections, are transplanted earlier, and have a dramatically improved survival outcome regardless of the donor match, conditioning regimen, and SCID type."

Buckley (2011) reported the long-term outcomes of 166 children who had received HSCT (follow-up 2 months to 28.3 years). It found that 94% of children transplanted during the first 3.5 months survived compared to 69% transplanted after 3.5 months of age.[36]

Chan et al. (2010) assessed outcomes based on parental responses to a survey. Survival was associated with being tested as a neonate, or identified prenatally using mutation information available from affected and carrier relatives (85% survival vs. 58% survival in infants not tested early) and earlier treatment. Infants who were treated and survived were, on average, treated at 29 weeks of age. Those who were treated but died were on average treated at 57 weeks.[37]

Gennery et al. (2010) analysed long-term outcomes of patients with SICD and non-SCID primary immunodeficiency disorders treated with HSCT in Europe between 1968 and 2005. Transplantation at a younger age was associated with better prognosis on multivariate analysis.[38]

Railey et al. (2009) assessed long-term outcomes after HSCT without conditioning and without post-transplant GvHD prophylaxis. It was also based on the results of a survey. In this study, 48 infants were transplanted in the first 3.5 months of life. Their survival rate was 96%, compared with 70% for the 113 transplanted after 3.5 months (8 year Kaplan-Meier survival).[39]

In addition, in a cost-effectiveness analysis (described in Criterion 16), Chan et al. (2011) administered a structured interview to obtain information on health outcomes to 39 consenting parents of SCID patients.[40] Thirty-two cases were sporadic, with no family history, and diagnosed late, with an average age at diagnosis of (mean $\pm$ SD) 9.0 $\pm$ 7.6 months (range 1.4 to 16.6 months). Eight of these infants died or were too ill to receive HSCT, and the average age at treatment (with PEG-ADA, one patient, or HSCT) in the remaining 23 children was 9.8 $\pm$ 5.5 months. Ten of the treated children died (one who had been treated with PEG-ADA and nine treated with HSCT). Seven children had a family history of SCID, and were diagnosed early: the mean age of diagnosis was 1.0 $\pm$ 0 months. HSCT was received by 3.7 $\pm$ 4.3 months, and all infants survived. Therefore, children who were diagnosed earlier were treated earlier and had better survival. Survey responses also indicated longer average hospitalizations before and after HSCT for SCID infants identified late (mean length of stay 30 days) compared to infants identified early (mean length of stay 14 days).

| Author | Population | Survival | Significant Findings |
|---|---|---|---|
| Brown (2011)[6] | -48 probands presenting between 1979 and 2009 and 60 siblings presenting between 1982 and 2010<br>-The median age at diagnosis of the probands was 143.5 days (range 1 to 455 days)<br>-4 of the siblings were diagnosed antenatally, the median age at diagnosis in the remaining cohort was 0 days (range 0 to 29 days) | -Overall survival in the proband cohort was 40%<br>-Overall survival in the sibling cohort was 90% | -The improved survival in the sibling cohort was irrespective of donor, conditioning regimen, or genetic defect<br>-Improved survival also seemed to be irrespective of date of transplantation (and hence not due to improvement in treatment with time): a subcohort analysis was performed of probands/siblings transplanted within 10 years of each other. In this subcohort, 54% of probands survived compared to 93% of siblings |
| Buckley (2011)[36] | -166 patients with SCID<br>-0 to 21 months at diagnosis | -Overall survival rate 76% (median follow-up 10 years, range 2 months to 28.3 years)<br>-94% transplanted during the first 3.5 months survive compared to 69% transplanted after 3.5 months of age | - "SCID recipients of allogenic, related [HSCT] in the neonatal period had higher levels of T-cell reconstitution and thymic output and a higher survival rate than those transplanted after 28 days of life" |
| Chan (2010)[37] | -126 families (158 SCID cases) | -Overall survival rate was 61%<br>- Infants tested as neonates, or identified prenatally using mutation information available from affected and carrier relatives, had a higher survival rate compared to those not tested early (85% vs. 58%) | -Infants diagnosed due to a positive family history had a mean duration of hospitalization that was almost 7 weeks shorter than unsuspected cases (12.2 vs. 18.8 weeks)<br>-The improvement in survival rate in infants tested as neonates or identified prenatally was not attributable to pre vs. post-2000 transplant or transplant donor type |

| | | | |
|---|---|---|---|
| | | - Infants who were treated and survived (n=78) were, on average, treated at 29 weeks of age. Those who were treated but died (n=20) were on average treated at 57 weeks | |
| Gennery (2010)[38] | -699 patients with SCID who underwent HSCT | -Overall 5-year survival 66.5%<br>-10-year survival in infants transplanted at <6 months 68%; 6-11 months 59%; over 12 months 51% | - Transplantation after 1995, at a younger age, B+ SCID phenotype, transplantation from genoidentical and phenoidentical donors, the absence of respiratory impairment or viral infection before transplantation were associated with better prognosis on multivariate analysis. |
| Railey (2009)[39] | -161 SCID patients 1982-2008 | -Overall survival 77% (median follow-up 8.7 years, range 6 months to 26 years)<br>-48 infants were transplanted in the first 3.5 months of life. Their survival rate was 96%, compared with 70% for the 113 transplanted after 3.5 months (8 year Kaplan-Meier survival) (p=0.002) | -"Those transplanted at <3.5 months of age had a superior survival rate, a lower rate of clinical problems, less need for booster transplants and better nutritional status." |

**Table 16: Evidence related to early treatment of SCID.**

*Survival after HSCT treatment*

Studies which assessed survival after HSCT are summarised in Table 17. We have included all studies, including those which assessed how different factors could affect survival and health outcomes including:

- Age and clinical condition at the time of diagnosis and of HSCT
- Degree of matching/HSCT donor:
    - HLA-matched sibling (matched related donor, MRD)
    - HLA-matched unrelated donor (MUD)
    - HLA-matched unrelated umbilical cord blood
    - HLA-mismatched related donor (MMRD)
    - HLA-mismatched unrelated donor (MMUD)
- Conditioning regimen
- GvHD prophylaxis
- SCID genotype/phenotype

100% survival was seen in some studies in patients who received HSCT from matched related donors (for example to a median age of 23.3 years).[41]

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| Brown (2011)[6] | -48 probands presenting between 1979 and 2009 and 60 siblings presenting between 1982 and 2010<br>-The median age at diagnosis of the probands was 143.5 days (range 1 to 455 days)<br>-4 of the siblings were diagnosed antenatally, the median age at diagnosis in the remaining cohort was 0 days (range 0 to 29 days) | HSCT | -Overall survival in the proband cohort was 40%<br>-Overall survival in the sibling cohort was 90% | -The improved survival in the sibling cohort was irrespective of donor, conditioning regimen, or genetic defect<br>-Improved survival also seemed to be irrespective of date of transplantation (and hence not due to improvement in treatment with time): a subcohort analysis was performed of probands/siblings transplanted within 10 years of each other. In this subcohort, 54% of probands survived compared to 93% of siblings |
| Buckley (2011)[36] | -166 patients with SCID<br>-0-21 months at diagnosis | -HLA-haploidentical or HLA-identical T cell depleted transplants<br>-No pre-transplant conditioning<br>-No post-transplant prophylaxis against GvHD<br>-2 patients were given | 76% (median follow-up 10 years, range 2 months to 28.3 years) | -Influences on survival include race and age at the time of transplant<br>-30/40 deaths occurred from viral infections<br>-No deaths due to GvHD. GvHD occurred in 45/149 patients given T cell depleted haploidentical parental marrow, 8 of 17 given HLA-identical marrow, and 4 of 5 |

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| | | cyclosporine for 1 month because of cutaneous GvHD from transplacentally transferred maternal T cells at presentation<br><br>-5 of the infants who received haploidentical marrow transplants also received unrelated placental blood transplants. 4 of the latter received pre-transplant conditioning, and were given post-transplant prophylaxis against GvHD | | given placental blood. In 45/57 cases this complication occurred when there was persistence of transplacentally transferred maternal T cells<br><br>-All of the T cells in 121/126 patients are of donor origin<br><br>-63/126 (50%) patients receive immunoglobulin replacement<br><br>-"SCID recipients of allogenic, related [HSCT] in the neonatal period had higher levels of T-cell reconstitution and thymic output and a higher survival rate than those transplanted after 28 days of life" |
| Chan (2010)[37] | -126 families (158 SCID cases) | -51% of patients received HSCT or enzyme replacement | -Overall survival rate was 61%<br><br>- Infants tested as neonates, or identified prenatally using mutation information available from affected and carrier relatives, had a higher survival rate compared to those not tested early (85% | -Infants diagnosed due to a positive family history had a mean duration of hospitalization that was almost 7 weeks shorter than unsuspected cases (12.2 vs. 18.8 weeks)<br><br>-The improvement in survival rate in infants tested as neonates or identified prenatally was not attributable to pre vs. post-2000 transplant or transplant donor type |

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| | | | vs. 58%)<br>- Infants who were treated and survived (n=78) were, on average, treated at 29 weeks of age. Those who were treated but died (n=20) were on average treated at 57 weeks | |
| Dvorak (2008)[42] | -15 children with SCID without a matched related donor (HLA matched or HLA-1 mismatched).<br>-The median age at HSCT was 5.7 months (range 0.5 to 16.4 months) | -Megadose of haplocompatible CD34+ cells and a fixed number of CD3+ cells from parent<br>-No myeloablative chemotherapy. Fludarabine administered to patients with maternal engraftment and evidence of GvHD<br>-No GvHD prophylaxis | 87% (median follow-up 39 months) | -T cell engraftment was seen in 73% of patients (12 patients)<br>-acute GvHD was seen in 58% of patients who engrafted after nonmyeloablative HSCT<br>-1 patient developed autoimmune haemolytic anaemia 5.5 months after a second myeloablative HSCT (overall incidence 8%)<br>-Clearance of pre-existing infections occurred after a median of 2.8 months<br>-Significant B cell engraftment (>5%) was seen in 25% of patients. B cell function developed in 33% of T cell engrafted patients (4/12), and they were able to stop intravenous immunoglobulin replacement |

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| Gennery (2010)[38] | 699 patients with SCID who underwent HSCT | HSCT using different sources of stem cells | -3-year survival with genoidentical donors (n=25) from 2000 to 2005 was 90%<br>-Survival using a mismatched relative was 66%<br>-Survival using an unrelated donor was 69% | -Transplantation after 1995, at a younger age, B+ SCID phenotype, transplantation from genoidentical and phenoidentical donors, and the absence of respiratory impairment or viral infection before transplantation were associated with better prognosis on multivariate analysis. |
| Marcus (2011)[43] | -13 patients with CD3δ deficiency who underwent HSCT<br>-7 patients were the first to be diagnosed with SCID in their family. Their age at the time of diagnosis ranged from 1 week to 14 months. The remaining 6 patients were diagnosed soon after birth because of already-diagnosed family member<br>- Mean age at transplant was 7 months (range from 1 | HSCT using different sources of stem cells as well as different conditioning regimens<br>-5 MUDs (3 bone marrow, 2 cord blood)<br>-8 related donors: 1 matched (bone marrow, 7 haploidentical (MMRD) (peripheral blood stem cells used in 5, bone marrow in 2)<br>-10/13 patients had conditioning (patients received cord blood and 1 patient who received MMRD were not | 62% (8/13 survived) | -Patients who received MUD-bone marrow transplant showed full reconstitution up to 20 years after HSCT<br>-Only 2 of 7 patients who received a mismatched related donor transplant survived<br>-Immunoglobulin levels appeared normal<br>-Acute GvHD occurred in most patients |

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| | to 23 months) | conditioned)<br>-GvHD prophylaxis was used in 10/13 patients | | |
| Mazzolari (2009)[44] | -74 infants with severe T cell immunodeficiency (including SCID) that underwent HSCT | -41 patients received MMRD-HCT (T cell depleted)<br>-19 MUD-HCT<br>-11 MSD-HCT<br>-2 PIRD-HCT (phenotypically identical related donors)<br>-Conditioning according to guidelines of the Inborn Errors Working Party of the European Bone Marrow Transplantation/European Society for Immune Deficiency in use at time of transplantation | 71.6% survival (surviving children had a follow-up of at least 5 years after HSCT) | -Recipients of HSCT from HLA-matched related donors had 100% survival and from unrelated donors had 86.4% survival compared to 51.6% survival in recipients of HSCT from mismatched related donors<br>-Most surviving patients attained robust T and B cell reconstitution: no immunological abnormalities observed in 67.3% patients<br>- 18.4% patients required substitution therapy with intravenous immunoglobulin at last follow-up visit<br>-55% showed one or more clinical problems at >1 year after HSCT: 31% had infections, 16% autoimmunity, 16% growth insufficiency, 18% neurodevelopmental and sensorial problems<br>-Risk of clinical complications influenced by donor type and by genotype. Persistence of a low number of circulating naïve T cells and long-term requirement for IV immunoglobulin were associated with a higher incidence of infections |
| Morio (2011)[45] | -88 patients with primary | -Umbilical cord blood | -71% 5-year survival for SCID (69% for all | -76% of all PID patients achieved stable |

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| | immunodeficiency (PID) between 1998 and 2008 (SCID n=40)<br>-Median age at transplantation of SCID patients 6.5 months (0-27 months) | transplantation (UCBT)<br>-No HLA disparity in 17, 1 in 15, 2 in 5, 3 in 3<br>-12 had no conditioning, 18 reduced intensity conditioning, and 10 myeloablative therapy | PIDs) | engraftment<br>-Pre-transplant infection, no conditioning, ≥2 HLA mismatches or diagnosis other than SCID, SCN (severe congenital neutropaenia) or WAS (Wiskott-Aldrich syndrome) were all associated with poor prognosis on multivariate analysis<br>-Reduced-intensity conditioning was associated with decreased overall mortality compared with myeloablative therapy |
| Neven (2009)[46] | -149 patients with SCID who had HSCT (1972 to 2004) | | -Overall survival rate 58%<br>-63% alive 2 years after HSCT<br>-Late onset mortality rate of 9% (8 patients died after 32.5 to 11 years) | -During long term follow-up of children that survived at least 2 years [followed for between 2 and 34 years (median, 14 years)], all had T cells of donor origin<br>-No decline in T cell immunity with time<br>-79% (65/82) surviving patients were off immunoglobulin substitution at last follow-up<br>-48% of patients experienced one or more significant clinical events (106 events), including persistent GvHD, autoimmune and inflammatory manifestations, opportunistic and non-opportunistic infections, chronic human papilloma virus (HPV), and a requirement for nutritional support<br>-With the exception of severe HPV |

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| | | | | infection, these complications tended to become less common 15 years later after HSCT<br><br>-Sixteen patients (15%) presented growth failure at some point in their follow-up<br><br>-Some patients also had psychosocial disabilities<br><br>-A multivariate analysis showed that the occurrence of adverse events correlated with non-genoidentical donors and acute GvHD, molecular diagnosis, especially diagnosis of Artemis SCID, and quality of immune reconstitution (T cell counts, quality of B cell reconstitution/persistence of immunoglobulin substitution)<br><br>-MSD HSCT transplant recipients had the best 15-year event-free survival rate. There was no difference between PRD (pheno-related)/URD HSCT and MMRD HSCT in terms of long term outcome |
| Patel (2008)[41] | -25 children with SCID (1981-1995)<br><br>-Median age at transplant 6.5 months (range 0.5 to 145 months), 12 with serious infection (20 | -Haploidentical T cell-depleted HSCT from mismatched related donors (20 children)<br><br>-Unmanipulated HSCT from matched related donors | Survival in patients who received HSCT from mismatched related donors 50% (to a median age of 15.2 years)<br><br>Survival in patients | -A higher frequency of long-term complications was present in patients who received mismatched related donor HSCT<br><br>-At the last follow-up, 7 of 10 survivors in the mismatched related donor group and 3 survivors in the matched related donor group had CD3+ T cell numbers within the |

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| | children treated HSCT from mismatched related donors)<br>Median age at transplant 1.8 months, 0.5-5.0 months, 1 with serious infection (5 children treated with HSCT from matched related donors | -No conditioning<br>-No GvHD prophylaxis | who received HSCT from matched related donors 100% (to a median age of 23.3) | normal range<br>-IgG levels were within the normal range in 8 of 10 patients evaluated in the MMRD group and 3 of 4 in the MRD group<br>- "Early transplantation of T cell-depleted MMRD bone marrow in infection-free, nonconditioned children with SCID results in long-term survival with a good quality of life." |
| Patel (2009)[47] | -23 HSCT SCID patients: 1998-2009<br>-The median age at first transplant for 23 SCID patients was 10 months [range 0.8-108] months<br>The average period of the last evaluation from the time of transplant was 38.9 months for 13 survivors who received MMRD/MUD and 70.0 moths for 5 survivors who received MRD transplants. 1998-2007 (compared to 1981-1995) | -5 HSCT from matched related donors<br>-18 HSCT from alternative donors (10 haploidentical mismatched related donor, 6 matched unrelated donor, 1 mismatched unrelated donor, 1 cord blood)<br>-19 patients received conditioning | -Overall survival 78.2%<br>-72.2% of patients receiving mismatched related HSCT, HSCT from a matched unrelated donor, HSCT from a mismatched unrelated donor and from cord blood survived (median follow-up 3.8 years)<br>-100% of patients receiving HSCT from matched related donors survived (median follow-up 7.5 | -Acute GvHD occurred in 2/18 mismatched related donor/matched unrelated donor group and 1 patient died<br>-Long term complications included respiratory diseases, dermatologic conditions, infectious complications, haematologic abnormalities, gastrointestinal disorder, speech delay, obesity and dental caries<br>-At last follow-up, 8/13 survivors in the mismatched related donor/matched unrelated donor group and 3/4 in the matched related group had CD3+ T cell numbers within the normal range<br>-5/13 (38%) of survivors in the mismatched related donor/matched unrelated donor group required intravenous immunoglobulin, and 1/5 in the matched |

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| | | | years) | related donor group<br>-HSCT in SCID patients resulted in a good quality of life for the majority of the survivors. All age-eligible children attend school<br>**-Comparison between SCID patients given conditioning or no conditioning (Patel et al. (2008)[41]:** Kaplan-Meier survival estimates at 1,3,5 years post-transplantation: cumulative survival of 7/10 (70%) for conditioned children who received HSCT from a mismatched related donor and 5/7 (71%) for conditioned children receiving HSCT from matched unrelated donors for all three time points. Without pre-transplant conditioning, survival of a comparable MMRD group was 13/21 (62%). The entire MRD group survived |
| Petrovic (2009)[48] | -31 patients with primary immunodeficiency disease (16 with SCID), since 1986<br>Patient follow-up 4 months to 20 years | HSCT (1 from a matched related donor and 15 haploidentical T cell depleted transplantation)<br>-8 patients with SCID received conditioning regimen with either their first or second transplant.<br>-Patients who received T | -Overall survival for SCID patients 63%, with the longest living survivor being 20 years post-transplantation | -"Better survival rates were observed in those patients transplanted at a younger age and free of infections, demonstrating that transplantation at an early age before significant infection, autoimmune manifestation and malignant transformation have occurred is beneficial." |

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| | | cell depleted grafts did not receive GvHD prophylaxis, all other patients did | | |
| Railey (2009)[39] | 161 SCID patients 1982-2008 | Related HSCT (10% HLA-identical) | -77% (median follow-up 8.7 years, range 6 months to 26 years)<br>- The survival rate for those who received haploidentical transplants is 75%, and HLA identical transplants is 100% | -48 infants were transplanted in the first 3.5 months of life. Their survival rate was 96%, compared with 70% for the 113 transplanted after 3.5 months (8 year Kaplan-Meier survival) (p=0.002)<br>-28 (76%) of the 37 deceased patients died from viral infections present at diagnosis<br>-One or more clinical problems were reported to have been present in the past two years in 71 (64%) of the survivors, although 95 (86%) are considered healthy by their families<br>-Intravenous immunoglobulin is being given to 64/111 patients (58%) and standing antibiotics are given to 30/111 (27%)<br>-The clinical problems reported as occurring in greater than 10% of the survivors included: persistent rashes in 25%, ADHD in 21%, sinusitis in 20%, asthma in 14%, diarrhoea in 14%, warts in 12% and height and weight below the 3rd percentile in 12%<br>-The clinical outcome differed among |

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| | | | | patients with SCID with different molecular defects |

**Table 17: Evidence related to survival after HSCT. Abbreviations: HPV, human papilloma virus; HSCT, haematopoietic stem cell transplant; GvHD, Graft-versus-Host Disease; UCBT, umbilical cord blood transplantation; MUD matched unrelated donor; MMRD, mismatched related donor; MSD, matched sibling donor; PRD, pheno-related donor. Potential overlap of populations included in studies was not assessed.**

**Evidence related to other therapies**

*Enzyme-replacement therapy*

Enzyme replacement therapy (ERT) with pegylated bovine ADA (PEG-ADA) can be used to replace ADA in patients with ADA-SCID. It can be performed by local physicians.[35] Only one study met the inclusion criteria of the full 2010 evidence review prepared for the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children: Chan et al. (2005).[4,49] We have not reviewed ERT as it is not curative. However, Gasper et al., (2009) describes the different treatment options for ADA-SCID, and a consensus management strategy is proposed, which was then included in the European Group for Blood and Marrow Transplantation and ESID guidelines (see Figure 5).[35] In this paper the demographics, length of ERT and survival for approximately 185 patients treated with PEG-ADA are described (April 1986-September 2008). They conclude that "PEG-ADA provides an often life-saving therapy at the time of diagnosis, when other options may be unavailable or less predictably effective. If ERT is continued beyond 6 months, there is a high probability that clinical benefit can be sustained for at least a decade. However, PEG-ADA may not easily be available in some countries, and its high cost is a barrier to long term ERT; and more uncertainty exists about how long-term immunologic and clinical benefit can be maintained beyond 8 to 10 years. An additional concern with ERT beyond 8 to years is the emergence of serious complications, including lymphoid and possibly hepatic malignancies, and progression of chronic pulmonary insufficiency."[35]

*Gene therapy*

Gene therapy was covered in the full evidence review.[4] Gene therapy using viral vectors has been trialled for the treatment of two types of SCID: X-linked SCID and ADA-SCID. Two case series of patients treated with gene therapy were included the evidence review: Hacein-Bey-Abina et al. (2002)[50] and Schmidt et al. (2005)[51]. The updated search identified four more publications, all of which reported extended follow-up results of infants treated with gene therapy. In all the studies, gene therapy was efficacious for the majority of patients (Table 18). In two studies, gene therapy was used in patients with ADA-SCID. In these studies, 100% of patients survived, and 9/10 and 4/6 recovered immune function.[52,53] Two studies assessed gene therapy for the treatment of X-linked SCID, one of which (Hacein-Bey-Abina et al. [2010][54]) included long-term outcomes of the infants included in Hacein-Bey-Abina et al. (2002)[50] and Schmidt et al. (2005)[51]. In one trial, 100% of patients survived with T cell repertoire restored in all patients, in the other trial gene therapy corrected immune dysfunction in 8/9 patients but one patient died during follow-up.[54,55] However, a total of five patients developed acute leukaemia (one in one trial, four in the other).[54,55] Leukaemia was the cause of death of the child who died.[54]

Trials using, new vectors, reportedly safer vectors for gene therapy are underway.[56]

Gene therapy could potentially be used to treat other forms of SCID, although for this type of therapy a molecular diagnosis is required.

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| Aiuti (2009)[52] | -10 children with ADA-SCID without an HLA-identical sibling donor<br>-Median age at gene therapy 1.7 years (range 0.6 to 5.6 years)<br>-4 children had had a failed mismatched related donor HSCT, 6 patients had had PEG-ADA for more than 6 months with inadequate response | -Retroviral-mediated gene therapy of CD34+ bone marrow cells<br>-Nonmyeloablative conditioning with busulfan (4mg/kg)<br>-Enzyme replacement therapy was discontinued 3 weeks before gene therapy (GT) and not given after infusion of the cells | -100% survival<br>-Median follow-up 4.0 years (range 1.8 to 8.0 years) | -9/10 had immune reconstitution with increases in T cell counts and normalisation of T cell function<br>-8/10 do not require enzyme replacement therapy, and have no signs of defective detoxification<br>-5/10 patients discontinued immunoglobulin replacement<br>-Serious adverse events included prolonged neutropenia (2 patients), hypertension (1), central-venous-catheter-related infections (2), Epstein-Barr reactivation (1) and autoimmune hepatitis (1) |
| Gaspar (2011)[53] | -6 patients with ADA-SCID without an HLA-identical family or unrelated donor and failure of effective immune recovery on ERT with PEG-ADA<br>-Median age at gene therapy 36 months (range 6 to 39 months) | -Gamma retroviral vector-mediated gene therapy of CD34+ bone marrow stem and progenitor cells<br>-Patients stabilised on ERT (between 6 and 36 months, median 15 months), but discontinued 10 to 30 days before gene therapy<br>-Myelosuppressive conditioning: 5 | -100% survival<br>-Median follow-up 43 months (range 24 to 84 months) | -4/6 recovered immune function with sustained evidence of gene-corrected T cells contributing to immune function<br>-In 2 patients, treatment failed. Both restarted ERT and remain well (low numbers of CD34+ cells harvested for GT in one patient, limited stem cell transduction in the other patient)<br>-3/6 remained off ERT therapy. One additional patient restarted ERT after gene therapy, but has since stopped ERT (40 months after GT and 34 months after restarting ERT). All four patients in which treatment was successful showed effective |

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| | | patients with 140mg/kg melphalan, one with 4mg/kg busulfan | | metabolic detoxification<br>-3/6 children have ceased immunoglobulin replacement<br>-All patients remained free of infection, and 2 cleared persistent CMV infection (present before GT)<br>-No adverse leukaemic side effects<br>-All children free from social restriction |
| Gaspar (2011)[55] | -10 patients with X-linked SCID without an HLA-identical family or unrelated donor<br>-Median age at treatment 10 months (range 4 to 46 months) | -Gamma retroviral vector-mediated gene therapy of CD34+ haematopoietic bone marrow stem and progenitor cells<br>-No conditioning<br>-After GT, patients were maintained on prophylactic immunoglobulin and antibiotic support until immunological recovery | - 100% survival<br>-Median follow-up 80 months (range 54 to 107 months) | -Functional polyclonal T cell repertoire restored in all patients (some variability observed)<br>-4/10 ceased immunoglobulin replacement<br>-One patient development acute T cell lymphoblastic leukaemia, treated by chemotherapy. The patient is now in remission<br>-All children free from social restriction |
| Hacein-Bey-Abina (2010)[54] | -9 children with X-linked SCID without an HLA-identical donor<br>-An additional patient | Described in Hacein-Bey-Abina et al. (2002)[50] | -89% survival<br>-1 patient died (median follow-up 9 years, range 8 to 11 | -GT corrected immune dysfunction in 8/9 patients<br>-7/9 patients had sustained immune reconstitution |

| Author | Population | Treatment | Survival | Other Significant Findings |
|---|---|---|---|---|
| | was treated in Australia and was described in a case report. Details of this infant were not included in all analyses | | years) | -6/9 patients ceased immunoglobulin-replacement therapy<br>-4/9 patients developed acute leukaemia, one died<br>-All patients had normal growth with respect to weight and height and attended regular schools. All patients except one did not have delays in their progression through school grades |

**Table 18: Evidence relating to gene therapy for the treatment of SCID. Abbreviations: GT, gene therapy; ERT enzyme replacement therapy; HSCT haematopoietic stem cell transplant.**

**Treatments used in screening pilots**

It is stated that in Massachusetts, in the majority of cases treatment of infants diagnosed with SCID will be HSCT.[22] "Prior to HSCT, the major focus of treatment is prophylaxis against routine infection and avoidance of live vaccines. In a smaller number of cases, and for only some types of SCID, treatment might consist of enzyme replacement therapy. In the infants with positive screens and abnormal follow-up testing who are found to have other immune deficiencies, the consulting immunologist will determine whether they might benefit from a wide range of preventative treatments or whether they do not require treatment."

Routes et al. (2009) and Verbsky et al. (2012) describe the treatments given to patients with different conditions identified during newborn screening in Wisconsin.[13,16] These are described in Crierion 13.

**Summary: Criterion 10 Met**

**There is an effective treatment with evidence that early treatment improves prognosis.**

## 11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

All patients with SCID require treatment. As described in Criterion 10, expert guidance on the recognition, diagnosis and management of primary immune deficiency diseases including SCID has been published.[30] The UK Primary Immunodeficiency Network also has a standard of care guideline for SCID.[33] The European Group for Blood and Marrow Transplantation and European Society for Immunodeficiencies (ESID) have produced guidelines for HSCT for primary immunodeficiencies, including SCID.[34]

However, treatment options for patients with low TREC numbers but without classical SCID are unclear. For example, Verbsky et al. (2012) discusses the dilemma of "what is the correct medical therapy in a child with isolated but profound [T cell lymphopenia], with no known genetic cause, and who does not have a SCID-defining infection due to early identification and prophylactic antibody replacement and antimicrobials."[16] They report that "although there is no clear consensus of what T cell count is consistent with SCID, a T cell count of less than 200 cells/μL is highly suggestive. When T cell counts are greater than 200 cells/μL with relatively normal T cell proliferative responses and no genetic cause, we initially take a 'watch and wait' approach over the first few months of life to determine if the T cell lymphopenia resolves. During this period of time, every effort is made to ascertain the genetic cause of [T cell lymphopenia]. In the absence of a defined genetic defect, we formally present each case to a panel of experts in [primary immunodeficiencies]/HSCT to aid in the decision to transplant while at the same time performing additional testing to help guide our ultimate diagnostic decisions."

In the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children report on the status of newborn screening for SCID they state that "the confirmatory tests used to follow up babies with abnormal newborn screen results, along with additional specialized immune testing, can help the paediatric immunologist to make decisions regarding the severity of immune dysfunction and the need for transplantation for these infants. These infants would not be picked up without newborn screening, and they are often in just as much need of significant treatment as the more well recognized SCID babies. In addition, some babies require supportive care with intravenous immunoglobulin (IV IgG) and antibiotics, even when a transplant is not needed."[10]

The evidence related to treatment of non-SCID T cell lymphopenias that may be detected by screening was not directly assessed. However, some guidance documents gave recommendations on the treatment of immunodeficiencies other than SCID; for example, Griffith et al. (2009) stated that "The risks of HCT must be compared with the expected long-term clinical outcome without HCT."[30] Non-SCID primary immunodeficiency diseases that are correctable by HSCT include:[30]

- Cartilage hair hypoplasia
- CD40 ligand deficiency
- Chediak-Higashi syndrome
- Chronic granulomatous disease
- Griscelli syndrome type 2
- Haemophagocytic lymphohistiocytosis
- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)
- Leukocyte adhesion deficiency type 1
- Wiskott-Aldrich syndrome
- X-linked lymphoprolifative syndrome
- Severe congential neutropenia
- MHC class II deficiency

The European Group for Blood and Marrow Transplantation and ESID also have guidelines for HSCT for other primary immunodeficiencies including: combined immunodeficiencies due to radiosensitive disorders such as DNA ligase 4 deficiency or Cernunnos deficiency, Nijmegen breakage syndrome; combined immunodeficiencies including Wiskott-Aldrich Syndrome, CD40L deficiency, Purine nucleoside phosphorylase deficiency, X-liked lymphoproliferative syndrome, Undefined T cell disorders, MHC class II deficiency, leukocyte adhesion deficiency, Oesteopetrosis; Chronic Granulomatous disease; Haemophagocytic disorders including Haemophagocytic lymphohistiocytosis, Chediak-Higashi syndrome, Griscelli, X-liked lymphoproliferative syndrome with Haemophagocytic lymphohistiocytosis.[34]

**Summary: Criterion 11 Met**

**All children with SCID will require treatment and there are polices on the recommended treatment of SCID. However the treatment pathways and guidelines for those children identified by screening with non-SCID T cell lymphopenias and in particular those that may not require HSCT, but who could receive immunoglobulin or antibiotics, is less clear.**

## 12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

**Summary: Criterion 12 Not Assessed.**

**Great Ormond Street Hospital London and Newcastle Hospital are the two UK centres for the management of SCID.**

## 13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened

No Randomised Controlled Trials were identified.

Comparing outcomes in states which piloted screening for SCID and other states in the US could provide useful information on the screening program. However, no such study was identified.

In the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children report which details the interim results of the US SCID pilot studies, it reports that all infants with immunodeficiency disorders have received treatment.[10] 80% of SCID patients have received HSCT and 20% are receiving enzyme replacement. The report does not detail the type of HSCT, the conditioning and/or prophylaxis regimen or at what age HSCT was performed. All treated infants were alive at the time of the report. The report states that "additional information regarding health outcomes is being collected and will be reported at a later date". In the report, it mentions that one infant with suspected SCID died before diagnosis was confirmed.[10]

Treatment of the five infants with SCID/severe T cell lymphopenia identified during the pilot screening program were reported in Verbsky et al. (2012).[16] These are shown in Table 19. Of the three children who received HSCT, the age at transplantation was not reported.

| Case | Treatment/outcome |
|---|---|
| 1. Rac2 | Umbilical cord transplant (5/6 match) with myeloablative conditioning<br>Alive, off immunosuppressants and intravenous immunoglobulin (for approximately 3 years) |
| 2. ADA | On enzyme replacement, gene therapy pending |
| 3. T-B-NK+ | Umbilical cord transplant (8/8 match) with myeloablative conditioning<br>Engrafted, alive |
| 4. T-B+NK+ | Transplant pending |
| 5. T-B+NK+ (IL-7 signalling defect) | HSCT from a matched unrelated donor (10/10 match)<br>Engrafted, alive |

**Table 19: Treatment of infants with SCID/severe T cell lymphopenia identified in Wisconsin between 2008 and 2011.[16] Age at transplantation and length of follow-up for each child not given.**

It is also reported, that up to 2011, all infants with low/absent TRECs (but not classical SCID) have remained free of significant infection in Wisconsin, which they attribute to the early initiation of antibody replacement, antimicrobial prophylaxis, and appropriate environmental controls.[11]

Longer-term, follow-up studies will provide information on whether the screening program is effective in reducing morbidity and mortality.

**Summary: Criterion 13 Not Met**

**No randomised controlled trials of screening were identified. Observational studies comparing long-term outcomes in US states that have piloted screening for SCID to states without screening might allow reductions in morbidity and mortality attributable to the screening programme to be assessed.**

## 14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

**Criterion 14: Not assessed**

## 15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

**Harms of screening**

The Lipstein et al. (2010) review found no studies that addressed harms associated with newborn-screening for SCID.[1] No further studies, published since 2008, on the harms of screening were identified. However, as with all screening tests there is likely to be harm from false-positive results and results with unknown clinical significance.

Carriers are not identified by the screening test. The presence of a family member with the disease could lead to the genetic testing of other members of the family and the identification of individuals carrying the mutation. This is likely to be the case whether screening is implemented or whether infants with SCID are identified due to presentation with symptoms, although more infants may receive a SCID diagnosis if newborn screening is implemented (i.e. fewer cases may remain undiagnosed).

**Harms of treatment**

Any harms associated with treatment need to be balanced by the finding that "without treatment of the underlying immunodeficiency, children with SCID die in early childhood from infection."[4]

*Harms of HSCT*

The Evidence review prepared for the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children found one paper that specifically focused on HSCT for SCID.[4] It analysed the rate of autoimmune haemolytic anaemia after treatment with HSCT for SCID, and found that 8/41 children developed auto-immune haemolytic anaemia, and 3 died from complications.

Adverse effects and clinical problems after HSCT were reported in some studies included in Table 17. These included:

- Graft versus host disease (GvHD)
- Autoimmunity and autoimmune haemolytic anaemia
- Infections, including HPV

- Persistent rashes
- Sinusitis
- Asthma
- Diarrhoea
- Warts
- Growth insufficiency
- Neurodevelopmental, psychosocial and sensorial problems

In addition, four studies were identified that looked at malignancies after HSCT,[57] or neurocognitive, social and behavioural outcomes after HSCT.[58-60] These are summarised in Table 20.

Kamani et al. (2011) looked at the occurrence of malignancies after HSCT for primary immunodeficiency disorders, including SCID patients. The 5-year, 10-year, and 15-year cumulative incidence of post-HSCT malignancy was 3% at 5 and 10 years and 3% at 15 years for SCID patients.[57]

Titman et al. (2008) described cognitive and behavioural abnormalities in children after HSCT. Children were compared to the general population and unaffected siblings. Children who had been treated with HSCT for congenital immunodeficiencies had lower IQ and emotional and behavioural difficulties. However, due to the study design these abnormalities cannot be associated with HSCT. Instead, socio-economic status, consanguinity, admission to paediatric intensive care unit and ADA-SCID were associated with worse IQ, and IQ and socio-economic status were the major determinants of behavioural outcome.[60]

Lin et al. (2009) looked at neurocognitive function after HSCT. There were significant decreases in mental development, psychomotor development and adaptive behaviour at some point post-HSCT. This reduction in scores was not due to loss of skills but a slowed rate of acquisition, as an analysis of raw scores showed an increase over time.[58]

Skucek et al. (2011) also assessed social functioning in children with congenital immunodeficiency and HSCT.[59] It found that HSCT "survivors were described by parents and teachers, but not themselves, as experiencing more difficulties with social functioning than the control group. Executive functioning was not associated with social functioning. However, an objective measure of physical appearance was significantly associated with social functioning."

*Harms of Gene Therapy*

Outcomes after gene therapy were presented in Table 18. In both of the studies of gene therapy for X-linked SCID identified, patients developed acute leukaemia.[54,55] In Gaspar et al. (2011), one of the 10 patients developed leukaemia.[55] The patient was treated with chemotherapy, and was reportedly in remission.[55] In Hacein-Bey-Abina et al. (2010), four of the nine treated patients developed leukaemia. Three patients were successfully treated with chemotherapy, but one child died.[54] These results included in Hacein-Bey-Abina et al. (2010)[54] were also included in the 2009 evidence review prepared for the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, based on Hacein-Bey-Abina et al. (2008).[4,61] No children who were treated with gene therapy for ADA-SCID developed leukaemia.

**Summary: Criterion 15 Partly Met**

**Harms from false positives have not been described. Harms associated with treatment need to be considered in the context that SCID is lethal in early childhood without treatment. The treatment options available to infants identified by screening are the same as for those diagnosed due to presentation with infection. The benefits and harms of HSCT treatment are well described. Gene therapy appears to increase the risk of acute leukaemia when used to treat X-linked SCID. Further study of this novel therapy is required to assess the balance of benefits and harms. The management of children with non-SCID T-cell lymphopenia will need to be agreed before the benefits and harms related to the overall screening and treatment pathway can be evaluated.**

| Author | Population | Treatment | Significant Findings |
|---|---|---|---|
| Kamani (2011)[57] | -2,266 primary immunodeficiency disorder patients (47% SCID) who had undergone allogenic HSCT between 1968 and 2003<br>-Ages ranged from 1.2 months to 47 years | HSCT | -The 5-year, 10-year, and 15-year cumulative incidence of post-HCT malignancy was 3% at 5 and 10 years and 3% at 15 years for SCID patients (and on average for all PIDD patients)<br>-Lymphoproliferative disorders, ranging from post-transplant lymphoproliferative disorders to non-Hodgkin lymphoma, were the most common malignancy<br>-T cell depleted bone marrow was a risk factor for the development of lymphoproliferative disorders |
| Lin (2009)[58] | -16 patients with SCID who survived beyond 1-year post-HSCT | -HSCT from halpoidentical or unrelated donor<br>-All patients received myeloablative conditioning | -There was a significant decrease 1 year post-HSCT in mental development (Bayley Mental Developmental Index [92.6 (pre) vs. 70.8 (1 year post), $p<0.0001$])<br>- There was no significant decrease in psychomotor development in the first year post-HSCT, but there was a significant decline from 1 year post to 3 years post (86.0 to 74.1)<br>-Adaptive behaviour (VABS) scores also significantly decreased during the first year post-HSCT [99.73 (pre) vs. 79.87 (1 year post), $p\leq0.0001$]<br>-Younger children (<8 months) had a more significant decrease in adaptive scores (VABS) compared with older children |
| Skucek (2011)[59] | -Patients with a congenital immunodeficiency (85% SCID)<br>-Children with ADA-SCID and Chediak-Higashi syndrome were | | -"[HSCT] survivors were described by parents and teachers, but not themselves, as experiencing more difficulties with social functioning than the control group"<br>-"Executive functioning was not associated with social functioning"<br>-"An objective measure of physical appearance was significantly associated with social functioning." |

| Author | Population | Treatment | Significant Findings |
|---|---|---|---|
| | excluded from the study<br>-Control group of healthy children matched for IQ, ethnic background, age and sex (group matching). | | |
| Titman (2008)[60] | -105 patients who had HSCT for severe congenital immunodeficiencies between 1979 and 2003 (41% SCID, 12% ADA-SCID)<br>-Control group of unaffected siblings<br>-Eligible participants had to be at least 3.5 years old at the time of assessment and at least 1 year after transplantation | | -The average IQ for the treated children was 85 (95% CI 81-90), significantly lower than both the population average of 100 and unaffected siblings<br>-Mean IQ Score for SCID patients 90.7, n=43<br>-Mean IQ score for ADA deficient SCID patients 64.9 SD, n=13<br>-Mean IQ score for SCID patients with expression of the defective gene confined to the immune system 96, n=27<br>-Multivariate analysis indicated that socio-economic status, consanguinity, admission to paediatric intensive care unit and ADA-SCID were associated with worse IQ<br>-25% of the cases scored above the threshold indicating clinically significant difficulties in emotion and behaviour, compared with 10% in the general population (parent-rated scores). Teacher-rated scores for 68 children showed that 24% of the cohort scored above the threshold indicating clinically significant difficulties<br>-IQ and socio-economic status were the major determinants of behavioural outcome after HSCT |

**Table 20: Evidence relating to harms of HSCT treatment**

## 16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource

The 2010 systematic evidence review of newborn screening and treatment of SCID found "limited evidence regarding cost or cost-effectiveness," and identified only one study that had assessed the cost-effectiveness SCID screening for the US population (Table 21).[1] Although the authors noted significant uncertainty in their model, they found an 86% likelihood of screening being cost-effective at a threshold of $100,000 per quality-adjusted life-year.

| Author, Study Design | Population | Significant Findings |
|---|---|---|
| McGhee et al[9] (2005), cost-effectiveness evaluation | NA | 86% likelihood of screening being cost-effective at a threshold of $100 000/QALY; threshold would be true with 61.2% false-negative rate and 3.2% false-positive rate; test cost of approximately $15, incidence of 1 in 125 000, and treatment cost of $1.35 million; assuming base-case scenario, the cost to identify and treat each case would be $485 000; implementation of screening would cost $23 920 000 and save 760 life-years per year of screening |

QALY, quality-adjusted life-year.

**Table 21: Evidence related to the cost effectiveness of SCID newborn screening identified in the 2010 systematic evidence review of newborn screening and treatment of SCID.[1]**

One further cost-effectiveness study was identified published since 2008 (Table 22). It created a Markov model to assess the cost-effectiveness of screening in the US.[40] However, this model also did not use results obtained during the pilot screening studies; instead, information for transition probabilities was obtained from a structured interview of 39 parents of patients diagnosed with SCID since 2000, comparing children diagnosed early due to family history with sporadic SCID cases. In addition, transition probabilities were obtained from the literature, and the national bone marrow registry, including published Kaplan-Meier curves. They estimated the cost of screening at $4.22 per test, based on machine usage, labour and reagents. The cost of confirmatory testing was estimated at "$250 per patient including complete and differential blood counts and lymphocyte phenotyping." Costs of HSCT were calculated from the Dana-Farber Cancer Institute, the Children's Hospital Boston and the Healthcare Cost and Utilization Project. The study found that screening for SCID is cost-effective: there was a 78% likelihood of screening being cost-effective at a threshold of $100,000/QALY. When SCID incidence was assumed to be 1/75,000 births and test sensitivity and specificity 0.99, screening remained cost-effective up to a maximum screening cost of $15 per infant screened. The cost and specificity of the screening test, the cost of the diagnostic test, the disease incidence and improved health outcomes with early treatment affected the cost-effectiveness.

As the authors point out, this cost-effectiveness analysis only considers SCID. "The benefits may be enhanced because the TREC assay detects non-SCID T cell lymphocytopenias in addition to SCID."[40]

| Author | Significant Findings |
|---|---|
| Chan (2011)[40] | -Over a 70 year time horizon, the incremental cost of screening was $5.44 per infant<br>-Universal screening in the US was estimated at $22.4 million/year with a gain of 880 life years and 802 QALYs<br>-Sensitivity analyses showed that cost and specificity of the screening test, the cost of the diagnostic test, the disease incidence and improved health outcomes with early treatment affected the incremental cost-effectiveness<br>-78% likelihood of screening being cost-effective at a threshold of $100,000/QALY<br>-When SCID incidence is assumed to be 1/75,000 births and test sensitivity and specificity 0.99, screening remains cost-effective up to a maximum screening cost of $15 per infant screened. |

**Table 22: Evidence related to the cost effectiveness of SCID newborn screening**

If approved, the TREC assay would be the first DNA-based screen to be added to the newborn screening panel. Both Wisconsin and Massachusetts have published how the screening process was implemented.[22,62] In the Wisconsin publication, they estimate the cost of testing equipment at $90,000 for a non-automated assay.[62] They report that two full-time chemists and two RT-qPCR systems can process 100,000 samples per year (including Guthrie card punching, all extraction/analysis steps, reporting, method, quality control and maintenance). Automation of the manual pipetting steps is expected to result in greater throughput. In Wisconsin, screening cost $630,000 from the development phase through the first nine months of screening (hiring additional staff, optimising test methodology, purchase of high throughput RT qPCR equipment and reagents, confirmatory testing by flow cytometry). The estimated cost of ongoing screening is $420,000 for 70,000 infants ($6/infant). The authors estimate that with 3 to 4 weeks hands-on training in the Wisconsin lab, another state newborn screening program could become fully operational within 6 months.

However, in the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children report on the status of newborn screening for SCID it states that budgetary concerns have delayed the implementation of SCID screening in some states (cost estimates for technology infrastructure reportedly estimated at $500,000 to $1 million).[10]

**Summary: Criterion 16 Uncertain**

**Cost effectiveness analysis has been undertaken in the US but the applicability of these studies to the NHS and translation of costs from the US insurance based system to a publically funded health system means that results should be treated with caution. The definition of what is cost effective might also differ.**

## 17. All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more

### cost effective intervention could be introduced or current interventions increased within the resources available

**Summary: Criterion 17 Uncertain**

**Other potential options for improving SCID outcomes include:**

- **Interventions to improve awareness of immunodeficiencies so that SCID is suspected and diagnosed in a timely manner**
- **Optimisation of HSCT protocols with regards to donor, conditioning regimen and prophylaxis based on evidence**

**No high quality research into the effectiveness of these alternatives was identified. However, as the mode of presentation is likely to be a severe infection, it is unlikely that increased awareness is going to make a substantial difference to the decision about screening.**

### 18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

No UK based publications were identified. However, there were publications based on the US program. Baker et al. (2010) described the logistical, technical and operational issues associated with implementing routine SCID testing, as well as the quality assurance, follow-up and cost-considerations for newborn SCID screening based on the Wisconsin pilot screening program.[62] Comeau et al. (2010) described the implementation of screening in Massachusetts.[22] In addition, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children report on the status of newborn screening for SCID gives information on the whole program.[10]

Quality control monitors in the Wisconsin screening program include:[62]

- Monitoring the slope of the calibration plot: a reproducible slope is consistent with good control of the analytical process
- Use of a "true zero control": whole blood spotted on filter paper from a known SCID infant (severe T cell lymphopenia confirmed by flow cytometry) or an adult blood sample depleted of naïve T cells (e.g. CD45RA+CD3+T cells). These zero controls monitor the method's performance in the critical area, and serve as a marker of potential cross-contamination

In the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children report on the status of newborn screening for SCID it states that an international database to assess laboratory performance has been created and that participation in a national US quality assurance program has enabled real-time quality improvement.[10] To support quality control measures, the CDC provides reference materials for within-laboratory quality control and between-laboratory proficiency testing. CSC laboratory support was described as part of the APHL webcast series.[63,64] As of April 2011, the tests showed 100% sensitivity and >99% specificity in 11 newborn screening laboratories.[10]

**Summary: Criterion 18 Not Met**

**Quality assurance systems in place in the US are described. No UK based reports were identified as screening is not currently provided in the UK. However, if screening was to be implemented in the UK plans for managing and monitoring the screening programme and quality assurance standards could be formulated based on the systems used in the US.**

## 19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

The current UK newborn screening program tests for:[29,65]

- Phenylketonuria
- Congenital hypothyroidism
- Sickle cell anaemia
- Cystic fibrosis
- Medium chain acyl-CoA dehydrogenase activity

A pilot expansion of the national newborn screening program is underway, and will test for

- Maple syrup urine disease
- Homocystinuria
- Glutaric acidaemia type 1
- Isovaleric acidaemia
- Long chain fatty acid acidaemia

These conditions can all be screened for using tandem mass spectrometry, a technique already utilised as part of the newborn screening program. The TREC assay for SCID, if implemented, will be the first DNA-based screen to be added to the newborn screening panel. Baker et al. (2010) estimate that two full-time chemists and two RT-qPCR systems are able to process 100,000 samples per year (including Guthrie card punching, all extraction/analysis steps, reporting, method, quality control and maintenance).[62] Automation of the manual pipetting steps is expected to result in greater throughput. The authors estimate that with 3 to 4 weeks hands-on training in the Wisconsin laboratory, another state newborn screening program could become fully operational within 6 months.[62] The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children report on the status of newborn screening for SCID states that pilots of TREC screening in states with a large number of births has provided evidence that TREC screening "is compatible with a high-throughput, automated environment", and sending samples from Louisiana to Wisconsin and Puerto Rico to Massachusetts for testing has shown the feasibility of this approach.[10]

Presently, it is recommended that advice on all cases of suspected SCID is sought from local immunologists in conjunction with the SCID specialist centres at Great Ormond Street Hospital or Newcastle General Hospital.[33] Children are transferred to Great Ormond Street Hospital or Newcastle General Hospital for diagnosis and treatment.[33] No publications detailing whether these centres have sufficient capacity were identified. The vignette produced by Professor Bobby Gaspar states that "the level of staffing for the diagnostic assays will need to be discussed."[5] It also states that:

"Presently, the two SCID referral centres in London and Newcastle will undertake the further testing, counselling and management of the identified patients. If incidence is significantly higher than anticipated and puts pressure on the existing service, expansion at the two main

centres may be required. However, this may not be necessary since transplantation of SCID diagnosed at birth is a less complex process."

**Summary: Criterion 19 Not Met**

**If implemented, the TREC assay will be the first DNA-based screen to be added to the newborn screening panel, and will require equipment for and expertise in RT-qPCR. No reports assessing the impact of a population screening programme on capacity within the current centres of expertise were identified. US publications detailing how screening programs were set-up in different US states are available, and could be used to guide UK set-up.**

## 20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children report on the status of newborn screening for SCID details the educational material relevant to screening and treatment of SCID and related T cell deficiencies.[10] It states that:

"To support families and to encourage the adoption of SCID newborn screening, the [immune deficiency foundation] launched several efforts, including a Web page for parents, a SCID newborn screening toolkit for use by families to educate policymakers, and a brochure to warn providers about the dangers of administering the live rotavirus vaccine to infants with SCID. The six pilot State newborn screening programs also created and distributed educational materials for the parents of newborns with a positive screen and/or a confirmed diagnosis. To support primary care providers and facilitate timely diagnosis and treatment, [the Health Resources and services Administration/Maternal and Child Health Bureau] funded the development of SCID clinical decision support materials, or ACT sheets, through its National Coordinating Centre for the Regional Genetic and Newborn Screening Service Collaboratives. As SCID newborn screening adoption increases, a directory of clinical specialists in pediatric immunodeficiencies and related T cell deficiencies will be developed for use by newborn screening programs, families, and health care professionals."[10]

No UK based information was identified. However, information on SCID, its causes and how it is inherited, the signs and symptoms, diagnosis and treatment is available from Great Ormond Street Hospital.[66]

**Summary: Criterion 20 Not Met**

**No UK evidence-based information explaining the consequences of testing was identified. However, if screening was to be implemented in the UK this could be based on the US publications.**

## 21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

No publications relating to public pressure were identified.

The International Patient Organisation for Primary Immunodeficiencies (IPOPI) has been campaigning for the implementation of SCID Newborn Screening in the European Union.[67] In

June 2011, the first Primary Immunodeficiency Forum organised by the IPOPI was held at the European Parliament.[68] Pilot SCID screening trials are reportedly taking place in Germany and Sweden.

The UK Primary Immunodeficiency Association has closed.[69]

**Summary: Criterion 21 Not Met**

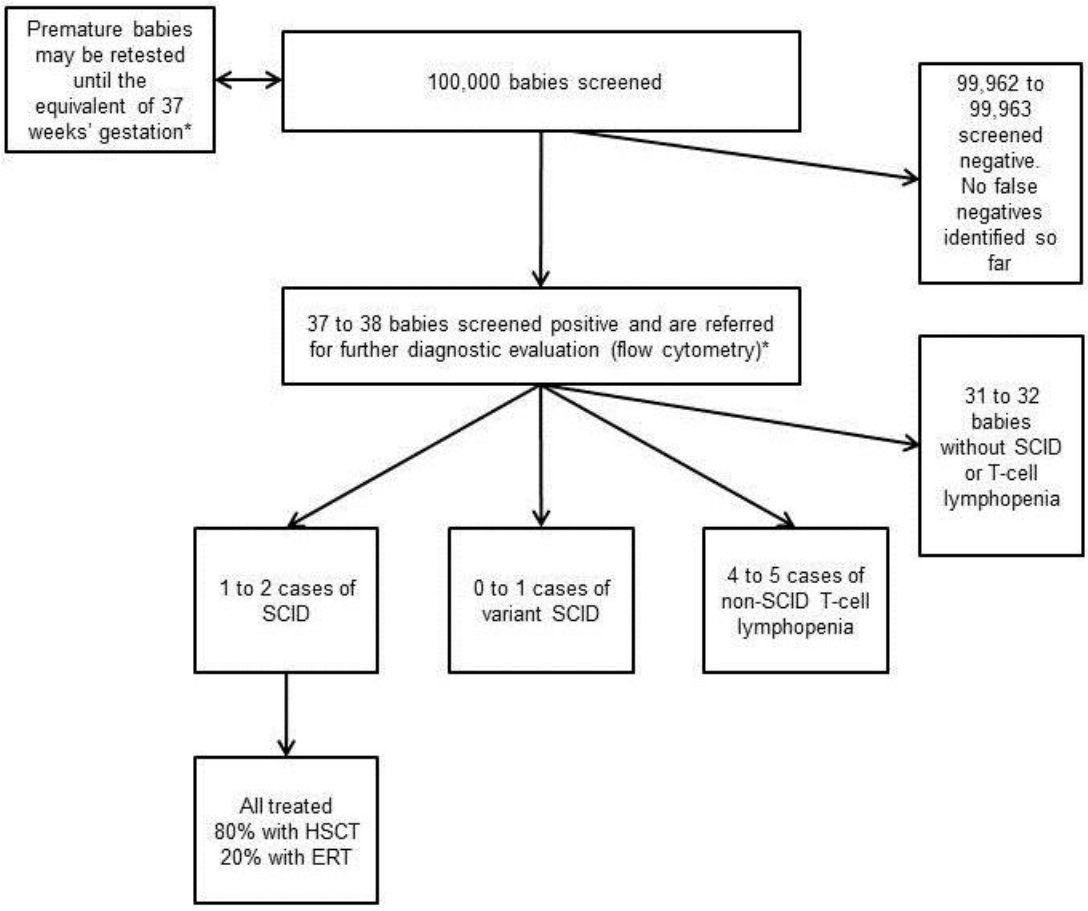
## 22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members

**Criterion 22: Not applicable**

## Screening flow chart

Based on the results of the pilot screening studies in the US, a flow chart of the screening process showing what happens to 100,000 babies screened is shown in Figure 6.

**Figure 6: Screening flowchart. Numbers are based on results of the US pilot screening studies collated for the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children report on the status of newborn screening for SCID.[10] Abbreviations: HSCT, haematopoietic stem cell transplantation; ERT, enzyme replacement therapy.**




***It should be noted that different pilot studies used different variations of the screening test (singleplex or multiplex); had different cut-off values; and had different policies with regard to premature infants- for example Wisconsin retested premature infants until they reached the equivalent of 37 weeks' gestation, while Massachusetts referred infants with a positive screening result for flow cytometry regardless of whether they were premature/in neonatal intensive care or not. The number of babies referred for flow cytometry may therefore vary depending on the screening policies adopted.**

## Conclusions

**The condition**

Severe combined immunodeficiency (SCID) is a group of disorders characterized by the absence of humoral and cellular immunity, caused by defects in T cell development. It is a genetic disease, which can be caused by mutations in a number of different genes. Left untreated, it is fatal in early childhood, due to the development of common and opportunistic infections. However, curative treatment options are available. The main treatment option is haematopoietic stem cell transplant (HSCT), although gene therapy has also been investigated as a treatment option for certain subtypes of SCID. Enzyme replacement therapy can be used to manage a specific subtype of SCID caused by mutations in ADA (ADA-SCID). It has been reported that 1 in 35,000 infants are diagnosed with the condition in the UK each year.

Children with SCID appear normal and healthy at birth, but develop infections and fail to thrive during the first months of life. In a recent study, children without a family history of SCID were diagnosed at a median of 143.5 days. A potential latent period exists between birth and the onset of infections during which the child may be asymptomatic.

In 2010 SCID was included in the US newborn screening core panel.

**The screening test**

The most intensively studied screening test for SCID is the T cell receptor excision circle (TREC) assay. TRECs are small, episomal DNA circles produced during differentiation of T cells. As SCID is a disorder of T cell development, TRECs are absent or present in low numbers with newborns with SCID. This test only identifies children with defects in T cell development: carriers of mutations are not identified. The screening test uses real time quantitative PCR to amplify TRECs from dried blood spots on Guthrie cards, which are already used for newborn screening. This test had been using in pilot newborn screening programs in the US, where it has been used to screen 961,925 infants (until 30$^{th}$ April 2011). The test demonstrated high sensitivity and specificity with no reported cases of SCID that have been missed by screening. However, the positive predictive value of the test is poor, identifying only 14 infants with SCID from 364 screen positives. This is partly due to the fact that SCID is a rare condition, but also because the test identifies children with other T-cell deficiencies or lymphopenias. False positive results are also often obtained from premature babies.

The distribution of TREC values in DBS in the population and cut-off values applied in the pilot studies in US states has been published. However, there have been no studies looking at TREC levels as a function of gestational age, and the US states in which screening was piloted treated positive TREC results from premature infants differently. In addition, the use of different methodologies (singleplex versus multiplex PCR) affects the TREC cut-off. The distribution of TREC values in the UK population will have to be determined and the cut-off value for SCID validated if a TREC assay is chosen.

If implemented, the TREC assay will be the first DNA-based screen to be added to the newborn screening panel, and will require equipment for and expertise in RT-qPCR.

Guidance on the clinical and laboratory diagnostic assessments that should be performed if SCID is suspected; and the policy on diagnostic tests used on screening-positive infants in the US pilot studies has been published. Diagnosis is confirmed by assessing the numbers of T cells, B cells and NK cells using flow cytometry. The place of gene sequencing is unclear.

**Treatment**

Great Ormond Street Hospital and Newcastle General Hospital are the treatment centres for SCID in the UK. There are polices and guidelines on the treatment of children identified with SCID. There is a wealth of evidence that supports HSCT as an effective treatment for SCID, with 100% survival after 20 years seen in some studies where patients have received HSCT from a matched a matched related donor. There is also evidence demonstrating better outcomes for children diagnosed and treated earlier. Gene therapy trials for SCID have also yielded positive results. However, in two trials of gene therapy for X-linked SCID children developed leukaemia.

**The screening program**

Harms from false positive screening results have not been described. The benefits and harms associated with HSCT and gene therapy have been well described, but need to be considered in the context that SCID is lethal in early childhood without treatment, and that the treatment options available to infants identified by screening are the same as for those diagnosed due to presentation with infection. However, as mentioned above, there is evidence that earlier diagnosis and treatment improves outcomes.

The screening program also identifies children with non-SCID T-cell lymphopenias. Treatments and the benefit of early treatment for these conditions was not directly assessed by this review. However the treatment pathways and guidelines for these children seem less well described. The management of children with non-SCID T-cell lymphopenia will need to be considered before the benefits and harms related to the overall screening and treatment pathway can be evaluated.

US cost effectiveness analyses of the screening program were identified, which concluded that screening is cost-effective. The applicability of these studies to the NHS and translation of costs from the US insurance based system to a publically funded health system means that results should be treated with caution.

It is unclear whether all other options for managing the condition have been considered. Other potential options for improving SCID outcomes include:

- Interventions to improve awareness of immunodeficiencies so that SCID is suspected and diagnosed in a timely manner
- Optimisation of HSCT protocols with regards to donor, conditioning regimen and prophylaxis based on evidence

No high quality research into the effectiveness of these alternatives was identified.

Quality assurance systems in place in the US are described. No UK based reports were identified.

If implemented, the TREC assay will be the first DNA-based screen to be added to the newborn screening panel, and will require equipment for and expertise in RT-qPCR. No reports assessing the impact of a population screening programme on capacity within the current centres of expertise were identified.

## Implications for research

The evidence update highlights areas where additional research could add value:

- A study of screening for SCID in pilot sites/states of the US to compare time to transplant and outcomes in infants identified by a population screening programme with those identified outside these programmes.
- A comparison of the different approaches in the US to determine the best approach to screening, for example:
    - Is the singleplex or multiplex RT-qPCR assay better?
    - Should actin or RNase P be used as a control?
    - What TREC cut-off should be used for a positive result?
    - What is the best approach to screening premature infants?
- Further research into the normal range of TREC levels in premature infants, and the determination of normal and abnormal TREC cut-offs as a function of gestational age
- Research into the management strategies for children identified by screening with abnormal levels of TREC and naïve T cells (with severe T cell lymphopenia), but more than 200 naïve T cells (outside classical definition of SCID), especially when they have novel, previously unidentified mutations. At what T cell threshold should HSCT be recommended?
- A systematic review of treatment options for severe T cell lymphopenia, and a review of the evidence regarding whether early treatment improves outcomes

# Methodology

## Search strategy

**BACKGROUND:** This is the first literature search on this topic for the UK National Screening Committee. There is no current policy or previous review documents.

In 2010 SCID was included in the US newborn screening core panel.

**SOURCES SEARCHED:** Medline, Embase, Cochrane Library.

**DATES OF SEARCH**: Medline 2002-December Week 3 2011; Embase 2002-2011 Week 52, Cochrane Library (Wiley Online Library) 2011 Issue 12 and 4.

**SEARCH STRATEGY:**

Medline (OVID interface)

1 exp Severe Combined Immunodeficiency/ (1726)

2 (severe adj combined adj (immuno-deficienc* or immunodeficienc*)).tw. (2281)

3 x-scid.tw. (75)

4 ((ada* or (adenosine adj deaminase*)) adj scid).tw. (57)

5 1 or 2 or 3 or 4 (3275)

6 exp Severe Combined Immunodeficiency/ep (25)

7 incidence/ or prevalence/ (233857)

8 (incidence or prevalence).tw. (452965)

9 7 or 8 (537486)

10 5 and 9 (125)

11 6 or 10 (139)

12 exp Severe Combined Immunodeficiency/di (181)

13 mass screening/ or neonatal screening/ (51151)

14 screen*.tw. (258474)

15 exp Polymerase Chain Reaction/ (269852)

16 polymerase chain reaction.tw. (112726)

17 pcr.tw. (229240)

18 (trec or trecs).tw. (342)

19 ((T cell or t-cell) adj receptor adj excision adj circle*).tw. (228)

20 or/13-19 (648317)

21 5 and 20 (412)

22 12 or 21 (543)

23 exp Severe Combined Immunodeficiency/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy] (829)

24 exp Anti-Infective Agents/ (1441760)

25 exp Immunoglobulins/ (287070)

26 exp Stem Cell Transplantation/ (39080)

27 antibiotic*.tw. (100060)

28 immunoglobulin*.tw. (50614)

29 (stem adj cell adj transplant*).tw. (19967)

30 exp Gene Therapy/ (30614)

31 gene therapy.tw. (25446)

32 enzyme therapy/ or enzyme replacement therapy/ (352)

33 enzyme replacement therapy.tw. (1532)

34 adenosine deaminase/tu (34)

35 or/24-34 (1793589)

36 5 and 35 (1660)

37 23 or 36 (1803)

38 11 or 22 or 37 (2137)

39 limit 38 to yr="2002 -Current" (1375)

40 limit 39 to human (1173)

A similar search was carried out in Embase, and a simplified version in the Cochrane Library.

**RESULTS**

All results were downloaded into a spreadsheet, and 610 duplicates removed.

A total of 1930 citations remained.

| **Database** | **No. citations retrieved** | **Exclusive** |
|---|---|---|
| Medline | 1173 | 1171 |
| Embase | 1364 | 758 |
| Cochrane Library | 3 | 1 |
| | **total =2540** | **Total = 1930** |

The title and abstracts of these citations, and where necessary and available the full text, were examined for relevance to neonatal severe combined immunodeficiency screening. 361 articles were identified as relevant. Selection criteria included:

Inclusion:

- Epidemiological studies of primary immunodeficiencies
- Screening programmes and tests
- Treatment options

Exclusion:

- Case reports identifying genetic mutations or describing novel presentations of SCID

The articles were categorised as follows:

| Category | No. of citations |
|---|---|
| Systematic reviews | 2 |
| Guidelines | 3 |
| Non-systematic reviews | 102 |
| Prevalence | 19 |
| Outcomes | 6 |
| Delayed diagnosis | 3 |
| Carriers | 3 |
| The test | 20 |
| Treatment – general | 5 |
| Treatment – antibiotics and immunoglobulin | 3 |
| Treatment – Haematopoietic stem cell transplantation | 96 |
| Treatment –novel | 75 |
| Screening | 24 |
| | |
| Total | **361** |

## Quality

Non-systematic reviews, editorials, other opinion pieces, reports of case series of fewer than four patients, articles with only adult subjects, and those with nonhuman data were excluded. Studies of immunodeficiencies not designated as SCID by The International Union of Immunological Societies Expert Committee for Primary Immunodeficiency (2011) were not included.[2] Additional relevant references identified during the preparation of the report were also included.

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