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Systematic reviews of screening for Severe Combined Immunodeficiency (SCID) in the NHS Newborn Blood Spot Screening Programme: Incidence, screening test characteristics and the effectiveness of treatments.

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List of Abbreviations

DBS	Dried blood spots
EPHPP	Effective Public Health Practice Project
IEM	Inborn errors of metabolism
LC	Liquid chromatography
MS/MS	Tandem mass spectrometry
NBS	Newborn blood spot
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NSQAP	Newborn Screening Quality Assurance Program
PHE	Public Health England
PPI	Patient and Public Involvement
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SCID	Severe Combined Immunodeficiency
TMS	Tandem mass spectrometry
UK NSC	UK National Screening Committee

Executive summary

Introduction

Severe combined immunodeficiency (SCID) is a rare treatable genetic disorder that affects the development of functional T cells and B cells in infants and if left untreated results in repeated severe infections and death within the first few years of life. At the present time, standard treatment for SCID is haematopoietic stem cell transplantation (HSCT), which is designed to restore immune function.

Age at transplant and history of infections are key confounding factors. Young age at time of transplant and being free from infections are associated with better outcomes after HSCT, therefore early diagnosis of SCID can greatly improve prognosis for those affected. Currently, diagnosis of SCID in the UK is made either through symptomatic presentation, or can be made before the onset of symptoms if there is known family history of the condition. Where there is known family history, SCID may be diagnosed antenatally or at birth.

Early diagnosis can potentially be made at birth by screening of newborns. This method measures the number of T-cell receptor excision circles (TRECs) in a dried blood spot, and has been shown in laboratory studies to have high sensitivity and specificity. Currently this test is not part of the UK Newborn Screening Programme. Pilot population-based screening studies have now been conducted in a number of countries, although to date not in the UK. 32 states in the US currently use TREC testing of Newborn Blood Spots (NBS) to screen for SCID. Results of this programme have been widely published (Kwan 2014), and demonstrate the sensitivity of the test in identifying SCID cases by population-based newborn screening. Whilst no cases of SCID have to date been shown to be missed by NBS TREC screening, the test also identifies non-SCID cases who have low TREC levels and T-cell lymphopenia (TCL) for other reasons. These include other congenital syndromes such as DiGeorge, Trisomy 21, and Ataxia-Telangiectasia, cases where the low TREC levels are due to other conditions such as cardiac or gastro-intestinal conditions, cases where the low TREC levels are due to the infants being pre-term and finally a group that have been identified as variant SCID.

The latest external review of screening for SCID for the National Screening Committee was produced by Bazian in 2012. This review drew on evidence from the Advisory Committee on Heritable Disorders in Newborns and Children in the US (Lipstein 2009), and from a systematic review of the current published literature using updated searches from a previous 2003 UK NSC report. Bazian 2012 included literature published between 2008 (the upper limit of the searches by Lipstein 2010) and 2011. In their conclusions they estimated a UK incidence of SCID of 1 in 35,000 infants. Their updated review provided further evidence supporting the high sensitivity and specificity of the TREC assay in screening for SCID cases, however they highlighted the poor positive predictive value of the test, with high numbers of false positives. This is due to the ability of the test to identify children with other T-cell deficiencies or lymphopenias, and from preterm babies.

The aim of the current review was to build on the previous work by Lipstein 2009 and Bazian 2012, to address the following 3 specific research questions:

1. What is the birth incidence of SCID and its subtypes?
2. What is the accuracy of the TREC test in population studies of screening for SCID?

3. Does early hematopoietic stem cell transplantation (HSCT) lead to improved outcomes compared with late HSCT in SCID patients?

This review was also designed to accompany a report by the same authors which reports on the health economics of screening newborns for SCID (Chilcott, 2017).

Methods

A systematic review of the relevant evidence was conducted to identify evidence to answer the three research questions. Due to the comprehensive reviews by Lipstein 2009 and Bazian 2012, it was not the intention to duplicate this previous work. Instead, search strategies were developed based on the Bazian review for questions 2 and 3, with studies sifted from 2011 so that any crossover between Bazian searches in 2011 and publication of their report in 2012 were accounted for. A new, separate search for incidence data was conducted, although it was anticipated that much of the incidence data would be identified through the screening studies. For treatment studies, all studies that met our inclusion criteria were extracted, regardless of their whether they had previously been included in Bazian 2012, as additional data was required for the modelling element of the report.

The following inclusion criteria were applied:

1) Incidence
   Population: All general populations not at high risk of inborn errors of metabolism.
   Target condition: SCID
   Outcome: Incidence of SCID and its subtypes
   Study type: Any systematic review, cross-sectional study or cohort study ideally taken over at least 5 years.
2) Screening test
   Population: Neonatal or newborn infants
   Target condition: SCID
   Intervention: The index test is the newborn screening for SCID using TRECs assay measurement of TRECs levels in dried blood spots
   Reference Standard: Flow cytometry, genetic testing and/or subsequent clinical detection of SCID
   Outcome: Sensitivity, specificity, predictive values
   Study type: Cross-sectional test accuracy studies, case control studies and cohort studies
3) Treatment
   Population: Patients with SCID
   Target condition: SCID
   Intervention: Early treatment with haematopoietic stem cell transplantation following screening (universal newborn screening, cascade testing or incidental detection)
   Comparator: Later treatment with haematopoietic stem cell transplantation following presentation of symptoms
   Outcome: Any outcome of treatment
   Study type: Any study design in humans

The following exclusion criteria were applied: Non-human studies; papers not available in the English language; letters; editorials and communications; grey literature and conference abstracts.

Searches of electronic databases were conducted in October 2016. The following databases were searched: MEDLINE; EMBASE; Cochrane Database of Systematic Reviews; Health Technology Assessment Database; Database of Abstracts of Reviews of Effects; Cochrane Central Register of Controlled Trials; and NHS Economic Evaluation Database. No date or language limitations were applied in the searches. Search results were de-duplicated across research databases and between individual research questions.

Results

Key question 1 (Incidence of SCID in the UK)

Description of the evidence

12 published studies containing non-UK SCID incidence data were identified through the electronic searches. Due to an absence of UK studies, an unpublished internal report documenting UK incidence data from the two UK centres for care (Great Ormond Street Hospital and Newcastle General Hospital) was also included in the review. Of the published studies, six were prospective, population-based studies of newborn screening programmes using TREC assay to detect SCID. Most of these studies were reports from the US screening programme (summarised in Kwan 2014). The remaining seven studies were retrospective, reporting SCID birth incidence. Incidence data for population-based studies was collected over a range of time periods, from 6 months (Kwan 2014 – Texas), to 60 months (Kwan 2014 – Wisconsin). The UK retrospective study reported data from a four year period (Gaspar).

Analysis of the evidence

The only non-US population-based study (Chien 2015 – Taiwan), reported a SCID incidence rate of 1 in 53,196 births. For the remaining US studies, incidence rates ranged from 1 in 3500 (Kwan 2014 – Navajo Nation) to 1 in 92,000 (Kwan 2014 - Texas). The overall SCID incidence rate for the US as reported by Kwan 2014 was 1 in 58,000 births. The high Navajo incidence rate is considered an outlier, consistent with the known founder mutation in the Navajo population. The UK data shows 82 cases of SCID over a four year period, suggesting a UK SCID incidence rate of 1 in 48,933 births. Some studies were identified that reported parental consanguinity (Al-Hertz 2015, Aghamohammadi 2014, Boussfiha 2014). High rates of parental consanguinity were associated with high SCID incidence.

A minority of studies documented incidence of SCID subtypes. Kwan 2014 report incidence of SCID subtypes across the US screening programme. Of 52 cases of SCID, 80.8% were typical SCID. The most common of these were ADA SCID, followed by RAG1 then JAK3. 17% of cases had leaky SCID, and 1.7% had Omen syndrome.

Kwan 2014 also report incidence of non-SCID TCL subtypes. 411 infants were identified with non-SCID T-Cell Lymphopenia. Amongst these, 33% had a recognised congenital syndrome associated

with T-cell impairment. The most common were DiGeorge, followed by Trisomy 21. 28.5% had secondary T-Cell impairment, and 28.5% had unspecified TCL. 7% of non-SCID TCL cases were preterm birth alone, with the remaining 2.9% having variant SCID.

Discussion

SCID is a rare condition and annual birth incidence is low. Because of this, incidence rates may fluctuate year on year, and longer time periods therefore provide a more accurate incidence rate. As the US newborn screening programme continues, longer periods of data collection become available. However, the current longest time period is 60 months, in Wisconsin (Kwan 2014), and this is the only study so far providing incidence rates based on population-based screening programmes over 5 years. At the time of the Bazian review (2012), a UK incidence rate of 1 in 35,000 was estimated, based on two years of data. Four year data from the same two centres is now available, and gives a slightly lower incidence of 1 in 48,933. TREC cut-off values varied between studies and this will have impacted on the reported incidence rates of non-SCID cases identified by the screening in population-based studies. The evidence does not currently indicate the proportion of non-SCID cases who would be clinically detected were they not identified through whole population-based newborn screening. The most reliable available evidence of the numbers of SCID subtypes and incidence of non-SCID TCLs comes from the Kwan 2014 summary of the US screening programmes. 20% of leaky SCID cases lacked a genetic diagnosis, despite extensive gene sequencing. In almost 15% of typical SCID cases identified, no mutation was found, with known SCID genes excluded. SCID may have previously been underdiagnosed in children with fatal infections. The data shows 411 other TCLs identified compared with 52 SCID cases. Rates varied between states even within T cell screening cut-off subgroups.

NSC criterion 1: Met.

The current estimate of UK SCID incidence is 1 in 48,933. SCID is a severe condition, which, if left untreated, is invariably fatal. Although rare, the severity of the condition makes SCID an important health condition.

Key question 2 (TREC Screening test)

Description of the evidence

15 studies retrieved from the electronic searches met the inclusion criteria. 11 pilot/feasibility studies included retrospective samples of known SCID patients. Four studies were prospective population-based studies. All four of these studies were from the US newborn screening programme, and as such there may be some duplication of data with the 2014 paper by Kwan, which

summarises results from each of the state screening programmes. The Kwan 2014 paper includes the screening of over 3 million children. There was a large variation in cut-off values, although most studies fell within the range 20 copies/µl to 40 copies/µl. The lowest cut-off in the US screening programme studies was 7 copies/µl (Michigan), whilst Texas initially set cut-off at 200 copies/µl, then redefined 'abnormal' as 150 copies/µl. Studies screened for SCID and non SCID TCLs.

Analysis of the evidence

TREC screening of newborn dried blood spots demonstrated high sensitivity. Of all studies that reported sensitivity all reported sensitivity of 100%. Specificity was also high, for example 99.98% was reported by Verbsky 2011. Proportion of abnormal tests was reported in several studies, with differences for pre-term and full term babies. Vogel 2014 report overall abnormal tests of 0.36%, whilst Chien 2015 report a lower figure of 0.02%. Referrals for flow cytometry depended on TREC cut-off levels. False positive rates, where initial screen was abnormal, but subsequent flow cytometry results were above abnormal cut-off were reported by state in Kwan 2014. The range of abnormal results by state is a reflection of the variation in TREC cut-off values. There were no false positives for the Navajo population in Mississippi. For the UK, Adams 2014 predicted a substantial fall in referrals to flow cytometry with a drop from 40 copies/µl to 20 copies/µl, from 7000 referrals to 280 referrals.

Screening for SCID resulted in the identification of both SCID and non-SCID T-Cell Lymphopenia cases. Incidental findings were reported in a number of studies. Kwan's 2014 summary of US screening describes the identification of 411 infants with non-SCID TCL, compared to 52 SCID cases. Of these, 136 (33%) had syndromes with T-Cell impairment, most commonly DiGeorge (78/136); Trisomy 21 (21/136) and ataxia telangiectasia (4/136). 28.5% of non-SCID TCLs were secondary T-Cell impairments (cardiac anomalies, multiple congenital anomalies, loss into third space, gastrointestinal anomalies, neonatal leukaemia or not specified). 28.5% were unspecified T-cell lymphopenias, 7% were preterm births only, and 2.9% were variant SCIDs. Kwan 2015 identified one patient who did not present with severe infections despite being identified with non-SCID TCL on the NBS screen. The patient did develop neonatal tetany due to primary hypothyroidism but this responded to calcium supplementation and the patient remained healthy and free of infections at 2.5 years of age.

Discussion

Previous reviews have shown newborn DBS screening for SCID to be highly sensitive. This finding is supported by the current evidence identified by this review. All known SCID cases were identified in all studies, both prospective and retrospective. Several of the studies in this review were pilot studies and TREC levels were manipulated over the course of the study. The evidence clearly shows that TREC cut-off threshold influences the number of abnormal findings and subsequent referral to flow cytometry. Few of the studies contained long term follow-up data, however, in the US screening programme data, none of the children tested was subsequently found to have SCID. A recent review by van der Spek (2015) calculated report positive predictive values for each of the states in the US screening program. Differences in positive predictive values were explained by the differences in screening algorithms. PPVs calculated by van der Spek 2015 support the evidence reviewed by Bazian 2012, showing that the TREC screening test for SCID has poor positive predictive value, with most values falling between 2% and 15% PPV, ranging from 100% (Navajo Nation, an outlier), to 0.8% (Texas).

The study by Adams 2014 attempted to identify the most suitable cut-off values were TREC screening for SCID to become part of the newborn screening programme. 138/700,000 repeat heel pricks were predicted to be needed per year, a rate of 0.019%. After testing a range of TREC cut-off values, with no SCID cases missed at any level, it was predicted that in the UK, a TREC cut-off value of 20 copies/µl would result in presumptive positives of 0.04%, which would result in 280 referrals to confirmatory testing per annum.

NSC criterion 4 and 5: The distributions of test values in the UK population have been tested by Adams 2014, and a suitable cut-off for a UK screening programme can be defined. Therefore **criterion 5 is met**. The Bazian review in 2012 preceded the Adams study, and concluded that criterion 4 was only partly met due to the poor positive predictive values seen in other countries. There is a simple and safe test for screening for SCID. It is highly sensitive and specific. However due to continued uncertainty around the actual numbers of false positives that may be identified in the UK through a screening programme, **criterion 4 is still considered to be partly met**. A population-wide pilot screening programme would give a clearer indication of these rates.

Key question 3 (Early vs. late HSCT treatment)

Description of the evidence

Twenty five studies were identified that met the inclusion criteria for the review. 22 of these were studies of HSCT for SCID patients, two were of gene therapy and one was a study comparing gene

therapy to HSCT. Most were retrospective cohort studies, following SCID patients at mostly single centres or in a few cases at multiple centres. Gennery 2010 presents data from 37 treatment centres. Age at diagnosis and age at transplant were described in most studies. Diagnosis was made at an earlier stage where there was family history of SCID, rather than where diagnosis was made after patients were symptomatic. Median age at transplant was shown to be earlier when diagnosis was by family history. Several but not all studies attempted to compare outcomes by early versus late transplant (e.g. Myers 2002, Brown 2011). Early transplant was commonly defined as less than 3.5 months. Brown 2011 compared a sibling cohort to a proband cohort as a proxy for early versus late, as siblings were likely diagnosed early, either antenatally or at birth.

The other common confounding factor described in the studies was donor matching. Differences in outcomes by donor match – i.e. matched, unmatched and related/unrelated donors were analysed in a number of studies. Conditioning regimen was also reported as a potential factor influencing outcome.

Duration of follow-up varied greatly, within and between studies, from 6 months to over 25 years. Survival was the most commonly reported outcome. A range of other long-term outcomes and complications were reported, with antibiotic use, infections, cGVHD, asthma, ADHD, HPV, and cognitive and developmental delay reported in some studies.

Analysis of the evidence

The evidence from the treatment studies in the present review support previous findings. Overall survival rates ranged from 46% (Giri 1994) to 100% (Cuvelier 2016). Age at transplant, time period of transplant, sibling/proband cohort, donor matching and history of infection were all shown to influence survival. Several studies analysed the effect of early versus late transplant on outcomes. Examples include Dell Railey 2009 reports 96% 8-year survival after early transplant compared to 70% for those transplanted late. Brown 2011 report 93% survival for the sibling group, i.e. those diagnosed antenatally or at birth, compared to 54% survival for the proband group. Betrand 1999 report 73% survival for transplant at less than six months compared to 54% survival for transplant at greater than 6 months. Myers reports 95% 5 year survival for early transplanted patients compared to 90% survival for those transplanted late. Pai 2014 not only demonstrated improved outcomes for those transplanted early, but also for patients with no history of infection. Active infection at the time of transplant was shown to reduce survival to 50%.

Outcome reporting for other complications was not consistent, however for those that did report other complications and long term outcomes, there was evidence that long-term complications persist in a minority of patients. These include neurologic and cognitive defects, infections, continued antibiotic use, HPV, ADHD amongst others.

The studies reporting gene therapy both reported high survival rates, although both studies only had small sample sizes.

Discussion

A number of factors were shown to influence the effectiveness of HSCT for SCID. No active infections or no history of infections also improved outcomes, as did matched donors. Early transplant is consistently shown to improve survival and other long-term outcomes. The evidence base is growing steadily, and is consistent. These findings support a need to diagnose SCID at as early age as possible, and before patients become symptomatic and develop infections.

NSC criterion 9 and 10: The evidence demonstrates that HSCT is an effective treatment for SCID, and that early treatment improves prognosis. **Criterion 10 is therefore met**. There are agreed existing standard of care guidelines issued by the UK Primary Immunodeficiencies Network, and guidelines for the treatment of PIDs, including SCIDs, with HSCT outlined by the European Group for Blood and Marrow Transplantation and European Society for Immunodeficiencies. These were outlined by Bazian 2012. The report proposed that because of this, **criterion 9 was met**, however the authors pointed out that guidelines for the treatment of patients with low TREC counts but without typical SCID were not clear at that time. Whilst these guidelines remain unclear, there are emerging attempts to develop treatment guidelines. A paper by Dorsey 2017 was published outside of the searches timescale for the current review, however this paper provides a framework for diagnosis and management of patients NBS-identified SCID and leaky SCID from California and other states. Patients with NBS-identified non-SCID T-cell lymphopenia were followed, including 28 syndromic patients and 5 infants with idiopathic lymphopenia, with no identified underlying cause. The authors highlight the need for long-term follow-up of these infants in order to identify underlying diagnoses when none has been possible.

1. Introduction

Severe combined immunodeficiency (SCID) is a rare treatable genetic disorder that affects the development of functional T cells and B cells in infants and if left untreated results in repeated severe infections and death within the first few years of life. Abnormalities in a number of different genes are implicated in the development of SCID, which cause deficiencies in both T and B lymphocytes (Buckley 1999). It is invariably fatal if left untreated, with patients presenting with repeated infections. For some genetic subtypes, gene therapy or enzyme replacement therapy are potential treatment options (Fischer 2011), although enzyme replacement therapy is not curative but can be used to stabilise symptoms. However at the present time, standard treatment for SCID is haematopoietic stem cell transplantation (HSCT), which is designed to restore immune function.

A number of confounding factors have been shown to modify the effectiveness of HSCT. Donor matching is a key factor, with HLA-matched relatives offering the best chance of successful outcomes. Where there is no HLA-matched relative, HSCT may be performed with an alternative donor, for example T-cell depleted haploidentical related donor, or by utilising a pre-transplant conditioning regimen. Age at transplant and history of infections are additional key confounding factors. Young age at time of transplant and being free from infections are associated with better outcomes after HSCT, therefore early diagnosis of SCID can greatly improve prognosis for those affected. Currently, diagnosis of SCID in the UK is made either through symptomatic presentation, or can be made before the onset of symptoms if there is known family history of the condition. Where there is known family history, SCID may be diagnosed antenatally or at birth. Where no family history exists, the median age of diagnosis in children in the UK has been shown to be 143.5 days old (Brown 2011). Survival in this group of patients is reduced, compared to those diagnosed at birth, with many dying before transplant can be performed.

Early diagnosis can potentially be made at birth by screening of newborns. This method measures the number of T-cell receptor excision circles (TRECs) in a dried blood spot, and has been shown in laboratory studies to have high sensitivity and specificity. Currently this test is not part of the UK Newborn Screening Programme. Pilot population-based screening studies have now been conducted in a number of countries, although to date not in the UK. 32 states in the US currently use TREC testing of Newborn Blood Spots (NBS) to screen for SCID. Results of this programme have been widely published (Kwan 2014), and demonstrate the sensitivity of the test in identifying SCID cases by population-based newborn screening. Whilst no cases of SCID have to date been shown to be missed by NBS TREC screening, the test also identifies non-SCID cases who have low TREC levels and T-cell lymphopenia (TCL) for other reasons. These include other congenital syndromes such as DiGeorge, Trisomy 21, and Ataxia-Telangiectasia, cases where the low TREC levels are due to other conditions such as cardiac or gastro-intestinal conditions, cases where the low TREC levels are due to the infants being pre-term and finally a group that have been identified as variant SCID.

The latest external review of screening for SCID for the National Screening Committee was produced by Bazian in 2012. This review drew on evidence from the Advisory Committee on Heritable Disorders in Newborns and Children in the US (Lipstein 2009), and from a systematic review of the current published literature using updated searches from a previous 2003 UK NSC report. Bazian

2012 included literature published between 2008 (the upper limit of the searches by Lipstein 2010) and 2011. In their conclusions they estimated a UK incidence of SCID of 1 in 35,000 infants. Their updated review provided further evidence supporting the high sensitivity and specificity of the TREC assay in screening for SCID cases, however they highlighted the poor positive predictive value of the test, with high numbers of false positives. This is due to the ability of the test to identify children with other T-cell deficiencies or lymphopenias, and from preterm babies.

The report also highlights the wide range of distribution of TREC values used in newborn screening studies worldwide, including within the US screening programme. The authors point out the need to consider the most appropriate screening algorithms should the UK introduce this test into the UK screening programme. Importantly, the Bazian report highlights the lack of evidence surrounding the harms associated with false positive screening results. The authors found that whilst there was clear guidance on treatment policies for patients with SCID, that the treatment pathways for children identified with non-SCID diagnoses was less clear.

The aim of the current review was to build on the previous work by Lipstein 2009 and Bazian 2012, to address the following 3 specific research questions:

1. What is the birth incidence of SCID and its subtypes?
2. What is the accuracy of the TREC test in population studies of screening for SCID?
3. Does early hematopoietic stem cell transplantation (HSCT) lead to improved outcomes compared with late HSCT in SCID patients?

This review was also designed to accompany a report by the same authors which reports on the health economics of screening newborns for SCID.

1.1 Basis for current recommendation

The most recent UK NSC update review of screening for SCID was June 2012 (Bazian). The review contained evidence from an earlier systematic review prepared for the US Advisory Committee on Heritable Disorders in Newborns and Children published in 2010, in combination with evidence identified through updated searches, published between October 2008 (the upper limit of the systematic search performed for the earlier reports) and 2011.

1.2 Current update review and approach taken

The current review draws on evidence from 3 key search strategies: 1) Updates of the searches previously conducted and reported by Bazian 2012; 2) Searches conducted for a review by the authors of the current report in May 2015 (Chilcott et al 2016) - these searches were performed as part of a project with a primary objective to develop a cost-effectiveness model comparing the current situation (no screening) to a policy of screening for SCID within the UK newborn screening programme; 3) Searches from inception for any key question not covered by the Bazian 2012 review nor the Chilcott 2016 review. Taken together, these 3 search strategies were designed to ensure that all relevant evidence relating to each of the 3 specific research questions were reported, either in

the Bazian 2012 report, or the current report. Any new evidence identified during this process that significantly altered understanding of the 3 key issues was incorporated into the economic model developed by Chilcott et al 2016.

2. Aims

The aim of the evidence review is to examine three key questions relating to the effectiveness and appropriateness of newborn screening of TREC levels in DBS using TREC assay for SCID. The key questions for this project are shown in table 1:

Table 1. Specific Research Questions with NSC Criterion.

Key questions	**NSC criterion**
1. What is the birth incidence of SCID and its subtypes?	1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.
2. What is the test accuracy of the TREC test in population studies of screening for SCID?	4. There should be a simple, safe, precise and validated screening test. 5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
3. Does early hematopoietic stem cell transplantation (HSCT) lead to improved outcomes compared with late HSCT in SCID patients?	9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit

	for the individual screened then the screening programme should not be further considered. 10. There should be agreed evidence based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.

3. Methods

Public Health England provided PICO statements that described the precise scope of the three research questions and sub questions that needed to be addressed, along with their relationship to the NSC criteria. A systematic review of the relevant evidence based on these PICO statements was conducted. A combination of updated searches and searches from inception was used to identify studies.

3.1. Identification and selection of studies

The current report is an extension of work conducted by Chilcott 2016. Independent searches were conducted for this project in February 2016, in order to identify data for cost-effectiveness model parameters. However the current review aimed to ensure that no studies were missed as a result of variations in specific search strategies between the Bazian and Chilcott reviews. Therefore new, full searches were conducted. A separate, comprehensive search was undertaken to systematically identify literature for each of the three research questions. The search strategies were designed to combine previous searches from both the Bazian 2012 and Chilcott 2016 reports, and to update these to identify any new studies. Search strategies were therefore taken or adapted from Bazian 2012. Searches were conducted in October 2016. The full search strategies can be found in Appendix 1.

The following bibliographic databases were searched from inception to 11th October 2016:

- MEDLINE, MEDLINE In-Process and Epub Ahead of Print (OvidSP): 1946 to present
- EMBASE (OvidSP): 1974 to 2016 October 10
- Cochrane Database of Systematic Reviews (CDSR, Wiley Online): CDR 1996 to present
- Health Technology Assessment Database (HTA, Wiley Online): 1995 to present
- Database of Abstracts of Reviews of Effects (DARE, Wiley Online): 1995 to present
- Cochrane Central Register of Controlled Trials (CENTRAL, Wiley Online): 1898 to present
- NHS Economic Evaluation Database (NHS EED, Wiley Online): 1995 to present

No date or language limits were applied in the searches.

Search results were de-duplicated, and, due to crossover between research questions, also de-duplicated between research questions. The largest database, 'natural history with treatment' retained all the retrieved records. Therefore, all records were only sifted once, however data relevant to more than one key question may have been contained in one study. As a result, records may appear in more than one PRISMA flow chart. Where this is the case, these records are introduced as 'records from other sources', and flagged as originating from the 'natural history with treatment' database. Data from these records is reported in each relevant results section. Records retrieved from the searches for key questions 1 and 2, 'incidence' and 'screening', were sifted from inception. Records retrieved from the search for key question 3 'natural history with treatment' were sifted from 2011, to control for any possible time lag between studies identified by the Bazian searches in 2011 and publication of their report in 2012. As the current, updated search strategy differed slightly from the Chilcott 2016 searches, studies already identified in Chilcott 2016 are also introduced as 'records from other sources', in order to distinguish them from the new searches. Studies from both reviews were cross-referenced with each other. No studies contained in the Bazian 2012 review were found to have been missed by the Chilcott 2016 searches. However, subtle differences in inclusion/exclusion criteria between review mean that not all studies in Bazian 2012 are included in the current review. For example, conference abstracts were excluded from the current review, therefore those studies that were included in Bazian 2012 but were conference abstracts were excluded here.

Table 2. Inclusion and exclusion criteria for the three key questions

Key question	Inclusion criteria							Exclusion criteria
	Population	**Target condition**	**Intervention**	**Reference Standard**	**Comparator**	**Outcome**	**Study type**	
1) Incidence	All general populations not at high risk of inborn errors of metabolism.	SCID	None	None	None	Incidence of SCID and its subtypes	Any systematic review, cross-sectional study or cohort study ideally taken over at least five years	Non-human studies, papers not available in the English language, letters, editorials and communications, grey literature and conference abstracts.
2) Screening test	Neonatal or newborn infants	SCID	The index test is newborn screening for SCID using TRECs assay measurement of TRECs levels in dried blood spots	Flow cytometry, genetic testing and/or subsequent clinical detection of SCID	None	Sensitivity, specificity, predictive values	Cross-sectional test accuracy studies, case-control studies and cohort studies	Non-human studies, two gate study designs, papers not available in the English language, letters, editorials and communications, grey literature and conference abstracts.
3) Treatment	Patients with severe combined immunodeficiency	SCID	Early treatment with hematopoietic stem cell transplantation following screening (universal newborn screening, cascade testing or incidental detection)	None	Later treatment with hematopoietic stem cell transplantation following presentation of symptoms	Any outcome of treatment	Any study design in humans	Non-human studies, papers not available in the English language, letters, editorials and communications, grey literature and conference abstracts.

TRECs T-cell receptor excision circles; SCID Severe combined immunodeficiency.

3.2. Review strategy

Two reviewers (CGC and JL) screened the titles and abstracts of all records identified by the searches between them. Ambiguities or disagreements were resolved through consensus or discussion with the modeller (AB). Full copies of all studies deemed potentially relevant were assessed for inclusion by one reviewer (CGC). Ambiguities were resolved by consensus or discussion with a second reviewer (JL) and the modeller (AB). Further inclusion validation checks were made by cross-referencing studies against previous reviews – Bazian 2012, Lipstein 2010 and Van der Spek 2015.

3.3. Data extraction strategy

An electronic, piloted data extraction form was used to extract data by one reviewer (CGC). A second reviewer checked a sample of 20% of studies as a quality control measure (JL). Disagreements were resolved by consensus or discussion with the modeller (AB).

3.4. Assessment of study quality

Critical appraisal of studies was performed using standard quality assessment tools. Key questions 1 2 were evaluated using STARD checklist for diagnostic accuracy as due to the nature of reporting in the included studies, it was not possible to use QUADAS-2 to assess the index test against a reference standard. Critical appraisal of key question 3 was performed using the CASP checklist. Quality assessment was undertaken by one of two reviewers (CGC and JL); a second reviewer independently appraised the quality of a sample of 20% of studies. Disagreements were resolved by consensus or through discussion with the modeller (AB).

3.5. Methods of analysis/synthesis

A narrative synthesis of results is presented. No meta-analysis/pooling of statistical data was conducted. Results are presented by key question.

4 Results

4.1 Key question 1 (Incidence)

What is the incidence of SCID in the UK?

This relates to NSC criterion 1:

'The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.'

4.1.1 Description of the evidence

The PRISMA flow diagram for the screening of the incidence records is presented in figure 1. Electronic searches identified 432 records, with 116 records remaining after de-duplication between databases. These 116 records include 7 records also identified through the searches for the other 2 key questions. Another record was identified by input from a clinician. Thirteen full text articles were assessed and all but one of these were found to meet the inclusion criteria and were therefore included in the narrative synthesis. One study (Gaspar) was unpublished and as such did not meet the inclusion criteria. However, due to a lack of any other published UK data this was included. The majority of incidence studies were also identified in the TREC screening searches. Data from these studies that relates to screening is reported under objective 2.

4.1.2 Characteristics of included studies

12 published studies containing non-UK SCID incidence data and one unpublished report relating to UK SCID incidence were identified. Of the published studies, 6 were prospective, population-based studies of newborn screening programmes using TREC assay for SCID detection. The remaining 7 studies reported data from retrospective reviews of medical records reporting SCID birth incidence.

Prospective population-based studies.

Of the 6 population-based studies, 2 were pilot studies (Chien 2015, Kwan 2015). Chien 2015 screened 106,391 newborns, which represents 35-37% of all newborns in Taiwan. Kwan 2015 report SCID incidence from 2 Navajo Nation hospitals. The pilot study screened 1800 infants. This was further expanded to include an additional 6100 infants. All remaining population-based studies report US data (Kwan 2013, Kwan 2014, Verbsky 2011, Vogel 2014). Kwan 2014 reports incidence data from 11 separate State screening programs. Data for individual states as reported by Kwan

2014 is reported separately in the following tables as well as by total number of infants screened across the US. The Kwan 2014 paper therefore reports SCID incidence across the US from 3,030,083 infants. It should be noted that there is some duplication of data between the US studies. There is crossover in data in Vogel 2014 that is reported in Kwan 2014 (New York) and Verbsky 2011 (Wisconsin). Time period of data collection ranged from 6 months (Kwan 2014 – Texas), to 60 months (Kwan 2014 – Wisconsin).

Retrospective studies

6 studies from a range of countries report clinically detected cases of SCID using reviews of medical records: Al-Herz 2015 (USA and Kuwait); Aghamohammadi 2014 (Iran); Bousfiha 2014 (Morocco); Kilic 2013 (Turkey), Rhim 2012 (Korea); Gaspar (unpublished) UK. 1 further retrospective study reports prevalence of SCID subtypes in 5000 children screened using TREC assays over a 4 year period (Galal 2016, Egypt).

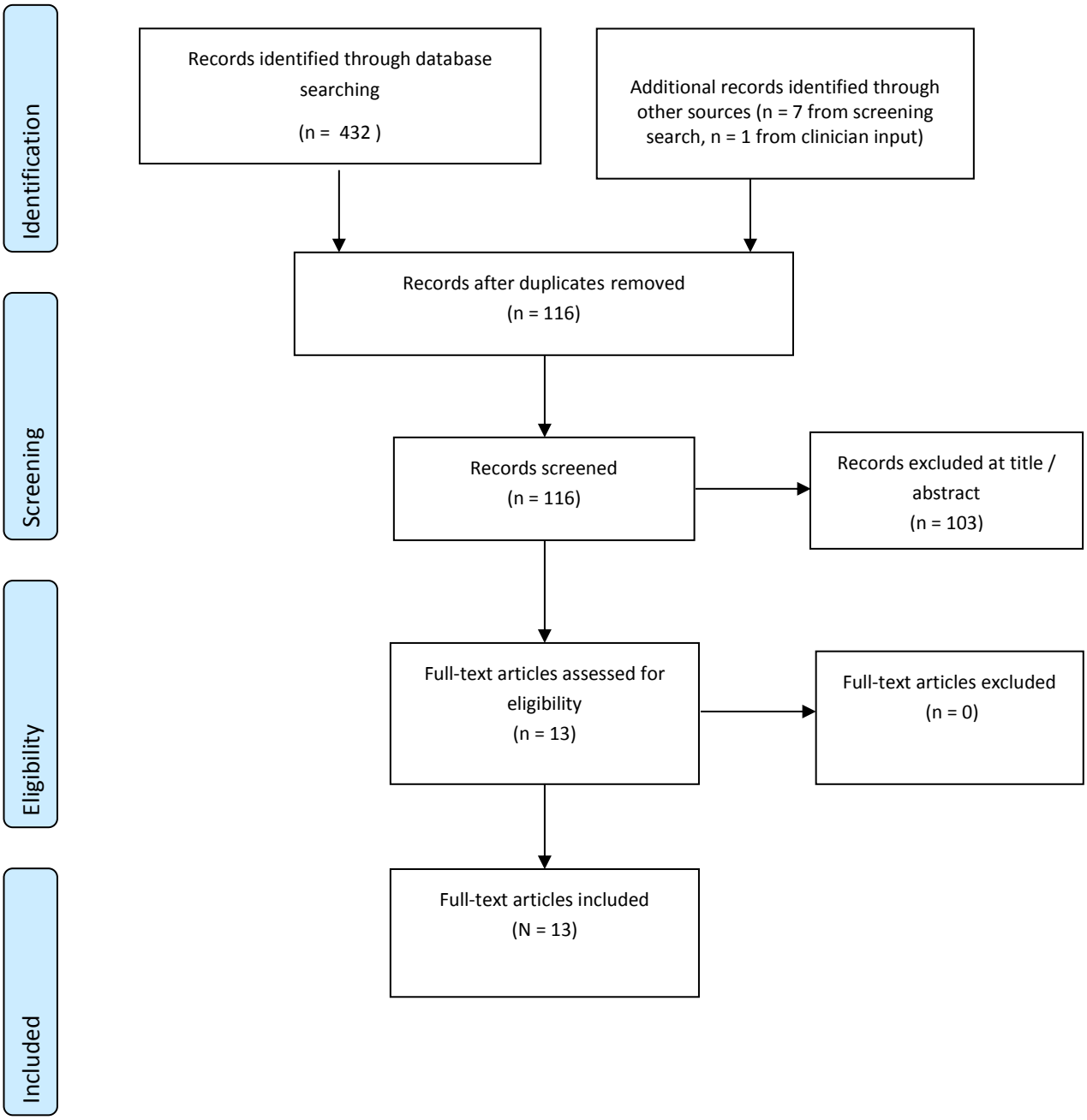
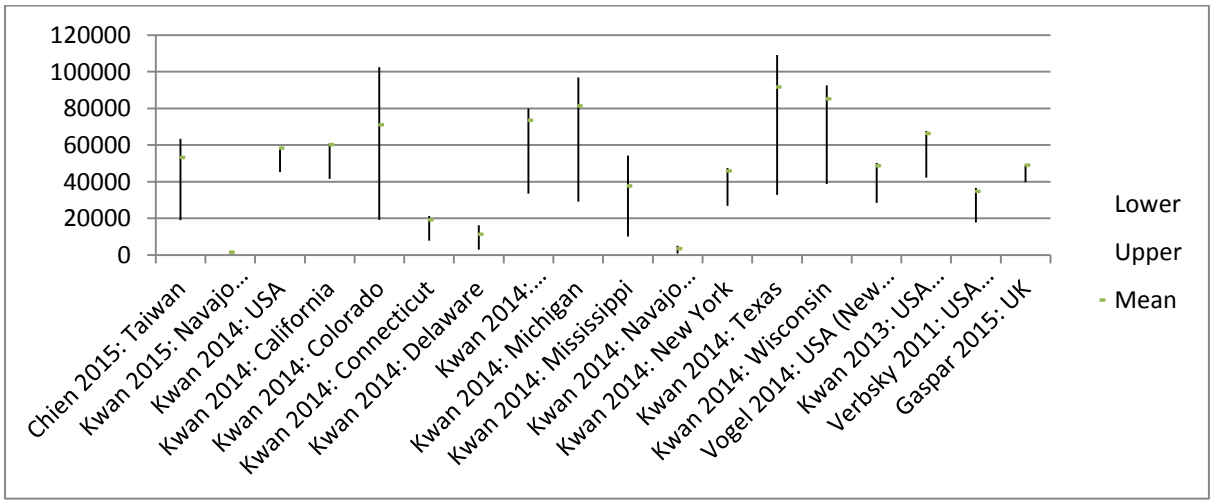


Figure 1. PRISMA Flow Diagram: Incidence of SCID

4.1.3 Analysis of the evidence

Incidence of SCID: The only non-US prospective screening study (Chien 2015, Taiwan), reported a SCID incidence rate of 1 in 53,196 births. Incidence rates for US screening studies varied by State. The highest incidence rates were those reported in studies of Navajo populations, with Kwan 2014 reporting a SCID incidence rate of 1 in 3500. This is noted as an outlier, consistent with the known founder mutation in the Navajo population. For the remaining US States, incidence rates were reported as 1 in 11,000 (Delaware); 1 in 19,000 (Connecticut); 1 in 38,000 (Mississippi); 1 in 49,000 (New York); 1 in 60,000 (California); 1 in 71,000 (Colorado); 1 in 73,000 (Massachusetts); 1 in 81,000 (Michigan); 1 in 85,000 (Wisconsin); and the lowest reported as 1 in 92,000 (Texas). Overall SCID incidence for the US is therefore reported by Kwan 2014 as 1 in 58,000 births. Of the published retrospective reviews of clinically detected SCID, only Al-Herz (2015) reports a SCID incidence rate, of 1 in 7500 births for Kuwait. For the UK, Gaspar (2015), reports an incidence of clinically detected SCID of 82 cases over a four year period, during which time there were 4,012,604 UK births. This represents a UK incidence rate of 1 in 48,934. Figure 3 shows incidence rates for published studies alongside the unpublished UK data.

Figure 2 - SCID incidence rates with confidence intervals



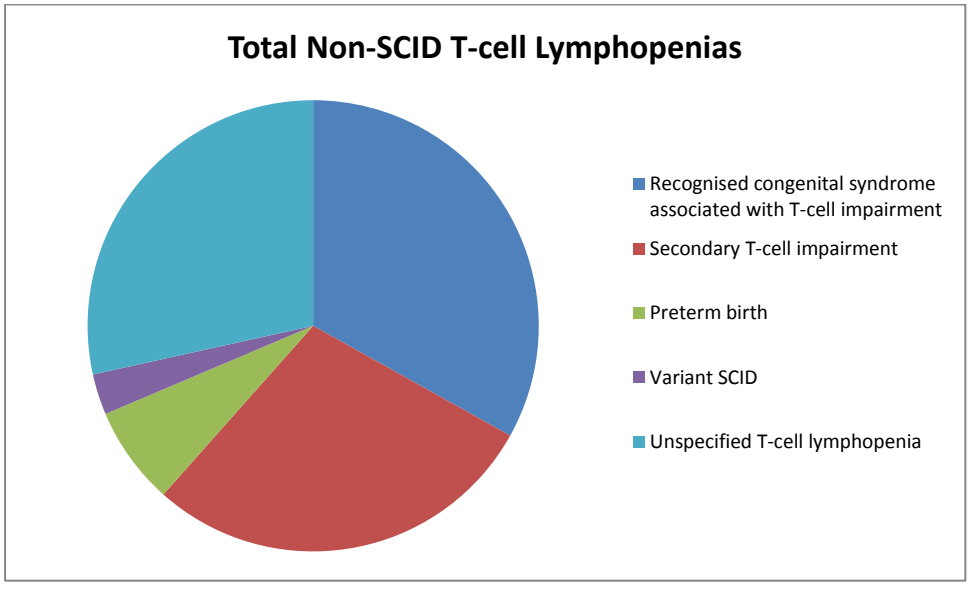
Parental consanguinity: 4 studies reported parental consanguinity. Galal 2016 (Egypt) reported 79.2% parental consanguinity in SCID patients; Al-Hertz 2015 reported rates of 94% in Kuwait, and 12% in the US. Aghamohammadi 2014 (Iran) reported 70.1% parental consanguinity, whilst the rate reported by Boussfiha 2014 was 35.1%.

Incidence of SCID subtypes: Kwan 2014 reports SCID subtypes detected across the US screening programs. Of 52 detected SCID cases, 80.8% were typical SCID (9.6% were ADA; 7.7% were RAG1;

5.8% were JAK3; 1.9% were DCLRE1C; 1.9% RAG2; 1,9% CD3D; 1.9% TC7A; 1.9% Pallister-Killian - no mutation was found in 11.5%; genetic testing was incomplete in 7.7%); 17% had leaky SCID (7.7% RAG1; 3.8% RMRP, 1.9% IL2G, 1.9% DCLRE1C – no mutation was found in 3.8%). The remaining 1.9% had Omenn Syndrome. Galal 2016 report 50.5% T-B-SCID, and 38.5% T-B + SCID. Of the 2 SCID cases detected by screening by Chien 2015, 1 was IL2RG and the other was RAG1. Kilic 2013 (Turkey) report 10% CD3G; 5% CD3 deficiency of unknown cause; 10% Artemis; 10% Gamma Common Deficiency; 10% RAG1; 40% T-B-SCID with unknown genetic cause; 15% T-B+SCID with unknown genetic cause. Rhim 2012 (Korea) report 25% X-linked SCID and 75% 'other SCID types'.

Incidence of TCL subtypes: Kwan 2014 report other TCL subtypes detected across the US screening programmes. 411 infants were identified with non SCID T-Cell Lymphophenia. Of these, 33% (n=136) had recognised congenital syndromes associated with T-cell impairment. Table 5 details the numbers of these, but the highest proportion were DiGeorge; followed by trisomy 21. Small numbers were ataxia telangiectasia; trisomy 18; CHARGE; Jacobsen; CLOVES; ECC; Fryns; Nijmegen breakage; Noonan; Rac2 defect; renpenning; TAR; not specified; or cytogenetic abnormalities. 28.5% (n=117) had secondary T-cell impairment; 7.05% (n=29) were preterm birth alone; 2.9% variant SCID; and 28.5% (n=117) were unspecified TCL. Chien 2015 report 16 other TCL subtypes. These included 12.5% idiopathic T-cell lymphopenia; 31.3% 22q11.2 microdeletion syndrome, and 56.3% other medical conditions. Figure 4 shows the distribution of non-SCID TCLs for Kwan 2014.

Figure 3 – Distribution of Non-SCID TCLs in US population-based screening studies Kwan 2014



4.1.4 Discussion: Question 1

The review identified 13 studies that reported incidence of SCID. Six of these studies were prospective population-based studies of newborn screening programmes. However, four of these were reports of individual US states, of which there was overlap with Kwan 2014. Reported incidence rates varied by State, ranging from 1 in 3500 to 1 in 92,000. Variation may be due to high consanguinity in certain populations, for example the Navajo Nations. The overall incidence rate for the US is 1 in 58,000. Al-Hertz 2015 report parental consanguinity of 12% in US SCID patients. The only population-based screening study identified that was not part of the US NBS screening programme was Chien 2015, a pilot study of 35-37% of the total population of newborns in Taiwan. This study reported a SCID incidence of 1 in 53,196 births. Seven retrospective reviews of medical records were also retrieved. Overall SCID incidence rate was only reported in one published study (Al-Hertz 2015), where a figure of 1 in 7500 births in Kuwait was reported. This high incidence rate is reflected by the high parental consanguinity rate in Kuwait, reported by the authors as 94%. UK incidence of SCID was obtained from unpublished data from patients diagnosed at two centres in the UK over a four year period (Gaspar). 82 cases of SCID over this period represents a UK incidence rate of 1 in 48,933 births. This is comparable to the overall US incidence rate. Whilst the UK data was not obtained from a full prospective population-based study, the data is likely to be comprehensive as it originates from the only two centres treating SCID in the UK.

The most reliable available evidence of the numbers of SCID subtypes and incidence of non-SCID TCLs comes from the Kwan 2014 summary of the US screening programmes. 20% of leaky SCID cases lacked a genetic diagnosis, despite extensive gene sequencing. In almost 15% of typical SCID cases identified, no mutation was found, with known SCID genes excluded. Kwan et al 2014 suggest that SCID has previously been underdiagnosed in children with fatal infections. The data shows 411 other TCLs identified compared with 52 SCID cases. Rates varied between states even within T cell screening cut-off subgroups.

SCID is a rare condition and the small number of cases may cause incidence rates to be likely to fluctuate year by year. The US data was collected over a range of time periods, from six months up to five years. The UK data was collected over a four year period and this enhances its reliability when compared to the two year UK data collected at the time of the Bazian review in 2012.

The last review of screening for SCID for the UK National Screening Council (Bazian 2012) concluded that criterion 1 ‘the condition should be an important health problem’ was met. This was based on a

presumed UK incidence rate of 1 in 35,000, with data coming from the two UK centres for care in 2008 and 2009. They also draw on the evidence that SCID is invariably fatal if left untreated. The UK incidence rate from the latest data is slightly lower, estimated at 1 in 48,934. This is based on four year UK data from the same two UK centres for care (Great Ormond Street Hospital and Newcastle General Hospital). This is a rare disease and as such a degree of fluctuation would be expected year on year.

Criterion 1: Met

The current estimate of UK SCID incidence is 1 in 48,933. SCID is a severe condition, which, if left untreated, is invariably fatal. Although rare, the severity of the condition makes SCID an important health condition.

Table summaries for SCID incidence (Objective 1)

Table 3 – Studies of prospective, population-based new born screening programmes using TREC assay for SCID detection.

Author	Country	Population	SCID screening detection	Clinically detected SCID	SCID Incidence
Chien 2015	Taiwan	106,391 newborns (35-37% of all newborns in Taiwan) between May 1st 2010 and December 31st 2011 (19 months).	N=2	N=2 (from non-screened population)	1 in 53,196 births.
Kwan 2015	USA	Data from two Navajo Nation hospitals from February 2012 to June 2012. A pilot study screened 1800 infants, which was expanded to another 6100 infants screened.	N=4	N=0	1 in 1580 births.
Kwan 2014a	USA	Present data from 11 screening programmes in the USA, reporting data on a total of 3,030,083 infants.	N=52	N=0	1 in 58,000 births.
Kwan 2014	California	Between August 16, 2010 and May 31, 2013 (34 months) 1,384,606 infants were screened.	N=23	N=0	1 in 60,000 births.
Kwan 2014	Colorado	Between February 1, 2012 and March 31, 2013 (13 months) 70,989 infants were screened.	N=1	N=0	1 in 71,000 births.
Kwan 2014	Connecticut	Between October 1, 2011 and May 1, 2013 (19 months) 57,136 infants were screened.	N=3	N=0	1 in 19,000 births.
Kwan 2014	Delaware	Between July 6, 2012 and June 30, 2013 (12 months) 11,202 infants were screened.	N=1	N=0	1 in 11,000 births.
Kwan 2014	Massachusetts	Between February 1, 2009 and January 31, 2013 (48 months) 293,371 infants were screened.	N=4	N=0	1 in 73,000 births.
Kwan 2014	Michigan	Between October 1, 2011 and March 31, 2013 (18 months) 162,528 infants were screened.	N=2	N=0	1 in 81,000 births.
Kwan 2014	Mississippi	Between January 1, 2012 and	N=1	N=0	1 in 38,000 births.

Author	Country	Population	SCID screening detection	Clinically detected SCID	SCID Incidence
		December 31, 2012 (12 months) 37,613 infants were screened.			
Kwan 2014	Navajo Nation	Navajo Nation spans throughout parts of Arizona, New Mexico, and Utah, where health care is provided through the Navajo Area Indian Health Service. Between February 1, 2012 and June 30, 2013 (17 months) 3,498 Infants were screened.	N=1	N=0	1 in 3,500 births.
Kwan 2014	New York	Between September 29, 2010 and September 28, 2012 (24 months) 458,912 infants were screened.	N=10	N=0	1 in 49,000 births.
Kwan 2014	Texas	Between December 1, 2012 and May 31, 2013 (6 months) 183,191 infants were screened.	N=2	N=0	1 in 92,000 births.
Kwan 2014	Wisconsin	Between January 1, 2008 to December 31, 2012 (60 months) 340,037 infants were screened.	N=4	N=0	1 in 85,000 births.
Vogel 2014	USA (New York)	485,912 infants born during 2 years, including White, Black, Hispanic, Asian and other ethnicities.	N=10 (n=2 White, n=2 Black, n=3 Hispanic, n=2 Asian and n=1 “Other”).	N=0	Approximately 1 in 48,500 births.
Kwan 2013	USA (California)	All newborns in California during 2 years were 993,724 infants including Hispanic, White, Asian, Black, Native American and other ethnicities.	N=15	N=0	1 in 49,700 births. Omenn syndrome 1 in 331,000 births, typical SCID 1 in 90,000 births, variant of SCID/CID 1 in 166,000 births.
Verbsky 2011	USA (Wisconsin)	Between January 1st 2008 and December 31st 2010, 207,696 infants were screened.	N=5	N=1	Not reported.

Table 4 – Retrospective studies reporting SCID birth prevalence/incidence

Author	Country	Population	SCID screening detection	Clinically detected SCID	SCID Incidence
Galal 2016	Egypt	5,000 children below 18 years screened using TRECs assays at Cairo University Pediatric Hospital between 2010 and 2014. Parental consanguinity was 79.2% (n=111) in SCID patients.	N=130	N=0	Not reported.
Al-Herz 2015	USA and Kuwait	Patients registered in The US Immune Deficiency Network registry or Kuwait National PID Registry from January 2004 to December 2014. Parental consanguinity in SCID patients was 12% in USA and 94% in Kuwait.	N/R	N/R	1 in 7500 births in Kuwait. USA not reported.
Aghamohammadi 2014	Iran	New PID patients who were diagnosed and registered in Iranian Primary Immunodeficiency Registry from 14 participant medical Centres from March 2006 to March of 2013. Total N=731. Parental consanguinity in SCID patients was 70.1 %.	Screening not conducted.	N=154 representing 21.1% of all cases.	Not reported.
Bousfiha 2014	Morocco	Infants referred to one centre for suspected PID between 1998 and December 2012. 2,100 referred patients. Parental consanguinity in SCID patients was 35.1%.	Screening not conducted.	N=37	Not reported.
Kilic 2013	Turkey	Patients diagnosed with PID from 2004 to 2010 at 2 universities; the number of	Screening not conducted.	T-B−SCID with unknown genetic cause Total n=8; % of total PIDS 0.6%.	Not reported

Author	Country	Population	SCID screening detection	Clinically detected SCID	SCID Incidence
		registered patients in these centres comprises almost 87.5 % of total registrations from Turkey.		T-B+SCID with unknown genetic cause Total n=3, % 0.2%	
Rhim 2012	Korea	Individuals under 19 years of age who were diagnosed with PID from January 2001 to December 2005 in 23 major university hospitals.	Screening not conducted.	N=4	Not reported.
Gaspar (internal communication)	UK	Patients diagnosed with SCID at Great Ormond Street Hospital and Newcastle General Hospital from 2008 to 2012. There were 4,012,604 births in the UK during this time.	Screening not conducted.	n=82	1 in 48,934

Table 5 – Numbers of SCID subtypes, other T-Cell Lymphophenia subtypes and incidence of PIDs.

Author	Country	SCID subtypes	Other TCL subtypes	Incidence of primary immunodeficiencies
Galal 2016	Egypt	n=46 (50.5 %) T-B-SCID, n=35 (38.5 %) T-B + SCID, no suficient data for categorisation of other infants.	Not reported	Not reported.
Al-Herz 2015	USA and Kuwait	USA: n=30 ADA, n=20 γc, n=11 RAG1/2, n=12 IL7Rα, n=19 others (including CID). Kuwait: n=4 ADA, n=23 RAG1/2, n=13 Artemis, n=12 others (including CID).	Not reported.	Not reported.
Chien 2015	Taiwan	n=1 IL2RG, n=1 RAG1	n=16 other TCL (n=2 idiopathic T-cell lymphopenia (molecular defects not identified), n=5 22q11.2 microdeletion syndrome, n=9 other medical conditions)	1 in 11,821 births.

Author	Country	SCID subtypes	Other TCL subtypes	Incidence of primary immunodeficiencies
Kwan 2015	USA	N=4 SCID-A	N=1 low TRECs and TCL associated with congenital anomalies during the pilot phase.	1 in 1580 births.
Aghamohammadi 2014	Iran	Not reported.	Not reported.	Not reported.
Bousfiha 2014	Morocco	Not reported.	Not reported.	0.81/ 100,000 inhabitants
Kwan 2014	USA	Total n=52 SCID cases. 42/52 with typical SCID (N=9 IL2RG, n=6 IL7RA, n=5 ADA, n=4 RAG1, n=3 JAK3, n=1 DCLRE1C, n=1 RAG2, n=1 CD3D, n=1 TC7A, n=1 Pallister-Killian, n=6 no mutation found, n=4 genetic testing not completed), 9/52 with leaky SCID (n=4 RAG1, n=2 RMRP, n=1 IL2G, n=1 DCLRE1C, n=2 no mutation found), and 1/52 with Omenn Syndrome.	**N=411** identified infants with non-SCID t-cell Lymphopenia. Of which, ***n=136*** *had a recognised congenital syndrome associated with T-cell impairment* (n=78 DiGeorge, n=21 trisomy 21, n=4 ataxia telangiectasia, n=4 trisomy 18, n=3 CHARGE, n=2 Jacobsen, n=1 CLOVES, n=1 ECC, n=1 Fryns, n=1 Nijmegen breakage, n=1 Noonan, n=1 Rac2 defect, n=1 renpenning, n=1 TAR, n=10 not specified, n=6 cytogenetic abnormalities*).* ***n=117*** *secondary T-cell impairment* (n= 30 cardiac anomalies, n=23 multiple congenital anomalies, n=15 loss into third space, n=15 gastrointestinal anomalies, n=4 neonatal leukaemia, n=30 not specified) ***n=29*** *preterm birth alone*, ***n=12*** *variant SCID,* ***n=117*** *unspecified T-cell lymphopenia*.	Not reported.
Kwan 2014	California	Not reported.	Not reported.	Non-SCID TCL: 1 in 32,000 births.
Kwan 2014	Colorado	Not reported.	Not reported.	Non-SCID TCL: 1 in 26,000 births.
Kwan 2014	Connecticut	Not reported.	Not reported.	Non-SCID TCL: 1 in 11,000 births.
Kwan 2014	Delaware	Not reported.	Not reported.	Non-SCID TCL: 1 in 3,700 births.

Author	Country	SCID subtypes	Other TCL subtypes	Incidence of primary immunodeficiencies
Kwan 2014	Massachusetts	Not reported.	Not reported.	Non-SCID TCL: 1 in 6,400 births.
Kwan 2014	Michigan	Not reported.	Not reported.	Non-SCID TCL: 1 in 2,100 births.
Kwan 2014	Mississippi	Not reported.	Not reported.	Non-SCID TCL: 1 in 13,000 births.
Kwan 2014	Navajo Nation	Not reported.	Not reported.	Non-SCID TCL: 1 in 3,500 births.
Kwan 2014	New York	Not reported.	Not reported.	Non-SCID TCL: 1 in 6,600 births.
Kwan 2014	Texas	Not reported.	Not reported.	Non-SCID TCL: 1 in 2,600 births.
Kwan 2014	Wisconsin	Not reported.	Not reported.	Non-SCID TCL: 1 in 8,100 births.
Vogel 2014	USA (New York)	4/9 T-B+NK+, n=2 ADA, n=1 common γ-chain, n=2 IL2RG mutations, n=1 mutation not identified	n=1 leaky SCID (n=1 T-B+NK+).	1 in 5,000 births.
Kilic 2013	Turkey	n=2 CD3G, n=1 CD3 deficiency of unknown cause, n=2 Artemis, n=2 Gamma Common Deficiency, n=2 RAG1, n=8 T-B−SCID with unknown genetic cause, n=3 T-B+SCID with unknown genetic cause.	Not reported.	Not reported.
Kwan 2013	USA	n=4 IL2RG, n=1 JAK 3, n=3 IL7R, n=4 RAG1, n=1 RMRP I, n=1 unknown	n=1 DiGeorge syndrome, n=3 leaky SCID or Omenn syndrome, n=6 variant SCID/CID	1 in 19,900 births.
Rhim 2012	Korea	N=1 X-linked SCID, n=3 other SCID types	Not reported.	Not reported.
Verbsky 2011	USA (Wisconsin)	n=1 RAC2, n=1 ADA, n=1 T-B-NK+, n=2 T-B+NK+	n=5 reversible TCL, n=4 22q11.2 deletion syndrome.	Not reported.

4.2 Key question 2 (TREC Screening test)

What is the test accuracy of the TREC test in population studies of screening for SCID?

This relates to NSC criteria 4 and 5:

4: 'There should be a simple, safe, precise and validated screening test.'

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

4.2.1 Description of the evidence

Figure 2 provides the PRISMA flow diagram for the screening test review. Electronic searches identified 697 records after de-duplication and sifting of only post 2011 records. One additional record was identified through input from a clinician. Thirty-two full text articles were assessed, of which 17 were subsequently excluded for not meeting the inclusion criteria. This left 15 studies which met the inclusion criteria and were included in the narrative synthesis. 11 of these were previously identified by Chilcott 2016. 3 were identified in the updated searches. Records previously identified and reported in the Bazian review are not reported here (n=11).

4.2.2 Characteristics of included studies

Characteristics of included studies are summarised in Tables 6 and 7. Of the total 15 studies, 11 studies included some retrospective analysis of known SCID samples using the TREC assay in dried blood spot analysis, either as part of a population-based screening pilot or comparing retrospective SCID DBS samples with fresh newborn DBS samples (Adams 2014, Jilkana 2014, [redacted] (Perkin Elmer confidential unpublished), Felipe 2016, Kanegae 2016, Audrain 2015, Chien 2015, Borte 2012, Kwan 2015, La Marca 2014, Somech 2014), and 4 were prospective population-based studies (Kwan 2014, Vogel 2014, Verbsky 2011, Kwan 2013). All four non-pilot prospective population-based studies report data from the US newborn screening programme. These are summarised in Kwan 2014 and there is therefore some duplication between data reported from these studies.

Studies including retrospective positive samples including pilot population-based studies: Jilkana 2014 and Adams 2014 conducted retrospective analyses on dried blood spot samples to determine the sensitivity of newborn DBS testing on a number of normal and known SCID positive samples. Jilkana 2014 tested 982 normal controls with 18 known SCID positive patients, whilst Adams 2014 tested 5081 normal Guthrie card samples with 18 known SCID positive samples. [redacted] (Perkin Elmer Confidential unpublished) tested leftover NBS samples from California. 990 routine newborn

samples were screened, which included 5 known SCID samples. Somech 2013 evaluated TREC and KREC counts in the peripheral blood of seven infants born in Israel in a one-year period, who were later diagnosed with SCID. Chien 2015 tested 106,391 consecutive samples from newborns in one hospital in Taiwan, representing 35-37% of total births. Kwan 2015 reports a pilot feasibility study of 1800 DBS samples, which was then expanded to a prospective screening programme at Navajo Nation maternity hospitals. Five known SCID and two known DiGeorge samples were analysed as controls. La Marca 2014 tested 50,000 newborns from one region in Italy to determine a protocol for incorporating adenosine and 2-deoxyadenosine testing into the newborn screening programme. The study included 9 genetically confirmed ADA-SCID patients. Felipe 2016 screened 5160 neonates born in three hospitals in Spain, along with seven known PID samples. Kanagae 2016 analysed 8,682 samples from children born at three hospitals and two clinics in Brazil. Audrain 2015 tested 5028 newborn dried bloodspot samples from one neonatal screening laboratory in France, alongside eight samples from known SCID patients. Borte 2012 compared 2560 newborn dried bloodspots with 18 SCID and 21 disease control samples.

Prospective population-based studies: The remaining studies report data from prospective population-based studies (although Kwan 2014 provides a retrospective and epidemiological description of a combination of data from screening programmes). These studies report data obtained as part of the US Newborn Screening Program (Kwan 2013, Kwan 2014, Verbsky 2011, Vogel 2014). Kwan 2013 reports data from 2 years of screening in one State (California), with an included sample of 993,724. Verbsky 2011 reports data from 207,696 infants in a two year period in Wisconsin, whilst Vogel 2014 reports data from 485,912 infants screened as part of the New York Program, also in a two-year period. Kwan 2014 reports data and retrospective analyses of data from 10 states plus the Navajo Area Indian Health Service. The study reports on a total sample of 3,030,083, although there was variation in the duration of the screening periods reported by state, ranging from 6 months (Texas) to 60 months (Wisconsin).

TREC cut-off values: There was large variation in the TREC cut-off values used, although most studies fell within the range 20 copies/µl to 40 copies/µl. Audrain 2015 set the initial cut-off at <156 TRECs copies/reaction, then calculated new cut-offs using the mean of all 99th percentiles of each run. This resulted in abnormal cut-off being <39 copies/reaction. Felipe 2016 did not report their cut-off values. Borte (2012) set a cut-off of <15 copies/µl. Adams 2014 set TREC cut-offs initially at 40 copies/µ, and then revaluated at 35, 30, 25 and 20 copies/µl. Whilst the data reported in Kwan 2014 was all obtained through the US Newborn Screening Program, there is still variation in the initial

TREC cut-off values used between states. The lowest cut-off was set at 7 copies/µl (Michigan). Verbsky 2011 (Wisconsin) increased TREC cut-off values from 25 copies/µl for year one to 40 copies/µl for the remaining 17 months due to low numbers of abnormal assays. Vogel 2014 (New York) considered TREC values of <200 copies/µl as abnormal, whilst Texas (Kwan 2014) initially screened at <200 copies/µl, then took a final average of <150 copies/µl to be abnormal or borderline. See tables 6 and 7 for study level descriptions of TREC assay and flow cytometry, and for details of screening algorithms, including cut-off values.

4.2.3 Analysis of the evidence

There was little variation between studies in the reported sensitivity of NBS testing. Of those studies that reported sensitivity, all reported sensitivity of 100%. Several studies reported numbers of abnormal or inconclusive tests, with some reporting rates of false positives (i.e. initial tests are non-normal but normal after referral for flow cytometry). Verbsky 2011 reports a false positive rate of 0.018% (specificity 99.98%). Kanegae 2016 reported that all known SCID samples and DiGeorge samples were detected. For rates of abnormal or inconclusive tests, Vogel 2014 reports a rate of 0.36% abnormal cases. Chien 2015 report abnormal rates of 24/105,864 (0.02%) abnormal (19 of which required repeat testing as originally inconclusive), and 0.4% inconclusive (including 19 subsequent abnormals). Kwan 2013 report a rate of 0.005% significant T-cell lymphopenia. Kwan 2014 reports results from a number of screening programs, and demonstrates that different TREC cut-offs result in different rates of referral for flow cytometry. In addition, definitions of T-cell lymphopenia differed by state/screening program and this results in variable rates of false-positive results. Examples of reported false positive rates (referred for flow cytometry after non-normal TREC screen but subsequent T cell levels by flow cytometry above program cut-off) range from 0 (Mississippi, Navajo Nation) and 19 (Massachusetts) to 61 (California) and 67 (Texas). For the UK, Adams 2014 report rates of predicted referrals by TREC cut-offs based on retrospective analysis of DBS samples at a range of TREC cut-offs. Referrals were predicted to fall substantially from 7000 where TREC cut-off is 40 copies/µl, to 280 referrals where TREC cut-off is 20 copies/µl.

Positive predictive values: Table 11 shows positive predictive values for SCID of TREC screening tests for the prospective population-based studies, as reported in van der Spek 2015. Whilst the Navajo Nation PPV of 100% was the highest, this was an outlier. The remaining PPVs ranged from lows of 0.8% (95% CI -0.3 to -1.9) (Texas) and 1.7% (95% CI 0.6 to 2.8) (New York) to 20% (95% CI -15.1 to 55.1) (Mississippi) and 13.6% (-0.7 to 28.0) (Connecticut). The only non-US study (Chien 2015) had a PPV for SCID of 8.3% (95% CI -2.7 to 19.4), comparable with the average US studies For non-SCID TCL

PPVs, two US states had 100% values – Navajo Nation and Mississippi. The lowest US non-SCID PPVs were New York with 18.3% (95% CI 15.0-21.6), and California with 31.1% (95% CI 23.9-38.2).

Incidental findings: Screening for SCID resulted in the identification of both SCID and non-SCID T-cell lymphopenia cases. Non-SCID T-cell conditions identified through screening are reported in a number of the studies. Felipe 2016 report two of five positive samples were preterm and remained under observation. One of the five died before diagnosis. Chien 2015 identified cases of five congenital heart diseases, one congenital cytomegalovirus infection and cases of 22q11.del. Of 411 infants identified with non-SCID TCL, Kwan 2014 reports 136 infants (33%) with syndromes with T-cell impairment, the most common of which were DiGeorge (78/136), Trisomy 21 (21/136), ataxia telangiectasia (4/136), and Trisomy 18 (4/136). They also identified 117 secondary T-cell impairments (28.5%) including cardiac anomalies, multiple congenital anomalies, loss into third space, gastrointestinal anomalies and neonatal leukaemia; 117 unspecified T-cell lymphopenias (28.5%); 12 variant SCID cases (2.9%), and 29 cases of preterm birth alone (7%). Verbsky 2011 identified infants with TLC with secondary causes including anatomic abnormalities of the lymphatics, multiple congenital anomalies, chromosomal abnormalities and presumed metabolic disorder. Vogel 2014 reported numbers of non-SCID TLCs. 27/97 infants with a clinically significant condition were diagnosed with a non-SCID syndrome of which 18 were DiGeorge Syndrome. Out of 17 secondary TLCs, there were two cases of Trisomy 21, three gastroschisis, two non-immune hydrops, three hydroplastic left heart, two Dandy Walker malformation, congenital heart defect, two TGA and congenital diaphragmatic hernia and one case of leukaemia.

4.2.3.1 Methodological quality of studies

It was not possible to compare the index test to a reference standard due to the nature of the studies reported. Studies only conducted repeat testing, flow cytometry or genetic testing on abnormal samples. Therefore quality assessment of studies using QUADAS was not possible. The methodological quality of each of the 15 included studies was instead assessed by STARD guidelines on completeness of reporting. Individual assessments are presented in appendix 2. All studies detailed the TREC assay and TREC cut-offs used. Most provided a rationale for the cut-off values. All of the population-wide studies reported genetic diagnoses of SCID where determined, and those studies also reported diagnoses of other TCLs. The main methodological issue was a lack of long-term follow-up of normal cases, meaning that whilst reported sensitivity rates are high, it is still unclear whether these give the full picture of whether any positive samples have been missed at screening.

4.2.4 Discussion

Newborn DBS screening for SCID has been shown previously (Bazian 2012) and in the current review to be highly sensitive. All known SCID samples were identified in all studies, using a range of cut-off thresholds. Several of the studies included in the current review were pilot studies testing the feasibility of DBS testing, and as such manipulated their cut-off thresholds over the course of the study. Lower cut-offs appear to retain sensitivity, reducing the need for referral to flow cytometry. Referrals to flow cytometry were relatively low across the US prospective population-based studies. Kwan 2014 reported a total of 1265 referrals out of over 3 million neonates screened, a rate of approximately 0.04%. Across individual US States, approximately 4% of referrals to flow cytometry resulted in detection of a SCID case, with a further 32% of referrals resulting in incidental non-SCID TCL cases. Few studies contained long-term data that follows up negative samples to gain an accurate picture of specificity. However, in the large-scale population-based screening paper by Kwan 2014, none of those who tested negative were subsequently found to have SCIDs. A recent systematic review by van der Spek (2015) discussed TREC screening for and incidence of SCID. The authors point out differences in positive predictive values between the States should be explained by the variation in screening algorithms, with TREC cut-off values ranging from 7 copies/µl (Michigan) to 252 copies/ µl (Massachusetts). Despite this variation, most cut-offs did fall into the range of 20-40 copies/ µl. Van der Spek (2015) report positive predictive values for each of the states in the US screening program. Differences in positive predictive values may be explained by the differences in screening algorithms. PPVs calculated by van der Spek 2015 support the evidence reviewed by Bazian 2012, showing that the TREC screening test for SCID has poor positive predictive value, with most values falling between 2% and 15% PPV, ranging from 100% (Navajo Nation, an outlier), to 0.8% (Texas).

Adams 2014 aimed to address a number of issues that would need to be overcome before introduction of newborn screening for SCID in the UK, in particular establishing a suitable TREC cut-off value. Their study tested a newly developed TREC assay for newborn SCID, by Perkin Elmer. After testing a range of TREC cut-offs from 35 copies/µl down to 20 copies/µl, results suggest a 0.04% presumptive positives using a cut-off value of 20 copies/µl, after duplicate testing, compared to a 1% presumptive positive value using the higher TREC cut-off of 40 copies/µl. This would lead to a referral figure of 280. This figure is slightly higher than the US data on presumptive positives (0.02%

California, 0.03% full-term Wisconsin), however a population-wide pilot study would yield a more exact figure of presumptive positives.

The last review of screening for SCID for the UK National Screening Committee (Bazian 2012) noted that criterion 5 ‘there should be a simple, safe, precise and validated screening test’ was only partly met. This was due to the poor positive predictive value of the TREC assay. The current review supports this original statement. There is clear evidence of the high sensitivity of the NBS TREC assay in detecting SCID cases. This evidence comes from the existing prospective population based screening program in the US, pilot population-based studies in a number of other countries, and from laboratory tests of known positive samples. However, even when low TREC cut-off values are used, the test identifies neonates with other TCLs. In addition, false positive results are found in preterm babies. The long-term prognosis and outcomes in these non-SCID cases is currently unclear, and more evidence in this area is needed.

Table 6 – Characteristics of prospective population-based studies

Author	Country	Population	Description of TRECs assay and flow cytometry	Screening algorithm
Kwan 2013	USA	DNA extraction and determination of TREC levels of DBS samples collected from all infants born during 2 years in California from 2010. 993,724 infants were screened.	DNA extraction by Generation DNA purification and elution solution (Qiagen Germany). Real-time PCR and measurement of TREC and human beta-actin copy numbers (Roche Diagnostics; GenScript). Venous blood immunophenotyping for lymphocyte subset determination.	TREC cut off set at ≤40 copies/µl. Samples below cutoff had repeat TREC with β-actin testing. Repeat samples positive if TRECs ≤25 copies/µl and normal β-actin values. Repeat samples with TRECs ≤5 and B-actin ≤5,000, TREC 6-25 and B-actin ≤10,000 and NICU patients with TREC 6-25 and B-actin>10,000 required a repeat heel-stick sample, or if it is already a second sample, recall for lymphocyte subset determination. Urgent positive samples (ie, those with undetectable or 1-5 TRECs/mL of blood with normal control b-actin copy numbers) triggered immediate recall of infants for flow cytometry.
Kwan 2014	USA	Results of newborn screening programs from 10 US states plus the Navajo Area Indian Health Service. Duration of screening results available varied by state, from 6 months (Texas) to 60 months (Wisconsin). Total of 3,030,083 infants were screened.	Individual programs report their own specific methods/program details. All measure TREC levels by PCR using DNA from dried blood spots.	TREC cut-offs varied by state.
Kwan 2014	USA, California	Program duration 34 months, 1,384,606 infants screened.	PerkinElmer Genetics. Venous blood immunophenotyping for lymphocyte subset determination.	Samples ≤40 copies/ µl had repeat TREC with β-actin testing. Repeat samples with TRECs ≤25 copies/ µl categorised as positive if β-actin values were normal. Flow cytometry obtained after one positive or 2 incomplete screening results.
Kwan 2014	USA, Colorado	Program duration 13 months, 70,989 infants screened.	Not reported.	Samples ≤40 copies/ µl had repeat TREC with β-actin testing. Repeat samples with <40 TRECs and

Author	Country	Population	Description of TRECs assay and flow cytometry	Screening algorithm
				>8,000 β-Actin copies/μL were categorised as positive; Samples with <40 TRECs and <8,000 β-Actin copies were inconclusive, and second dried blood spots were requested. Flow cytometry obtained after one positive or 2 incomplete screening results.
Kwan 2014	USA, Connecticut	Program duration 19 months, 57,136 infants screened.	Assay developed by the U. S. Centers for Disease Control and Prevention (CDC).	TREC copies <10/μL and RNaseP Cycle threshold (Ct) <28 reflexed to immediate immunological evaluation. TREC cutoffs were ≤30/μL for term and ≤25/μL for preterm infants. Samples with RNaseP Ct ≥28 were unsatisfactory and additional DBS were requested for re-testing. TRECs between 10 and 30/μL required repeat TREC measurement in a new punch before an immunology referral.
Kwan 2014	USA, Delaware	Program duration 12 months, 11,202 infants were screened.	CDC based assay.	Cutoff set at TRECs <27/μL. Cut-offs were Borderline (17-26 TRECs), Abnormal (4-16 TRECs) and Alert (No Ct – 3 TRECs). Samples from premature infants (<38 weeks) that were invalid, or had low TRECs, were repeated on a subsequent dried blood spot.
Kwan 2014	USA, Massachusetts	Program duration 48 months, 293,371 infants were screened.	Not reported.	504/μL whole blood in initial assay, 252/μL whole blood in repeat assay. Samples with undetectable TREC on initial specimen had immediate flow cytometry. TRECs <252/μL on initial assay were requested repeat DBS. Serial TRECs <252/μL had flow cytometry.
Kwan 2014	USA, Michigan	Program duration 18 months, 162,528 infants were screened.	Not reported.	TRECs ≤7 copies/μL and β-Actin Ct ≤30 referred to a designated immunology clinic for flow cytometry; samples with 7-11 TRECs/μL and β-Actin Ct ≤30 required a repeat sample. If a second

Author	Country	Population	Description of TRECs assay and flow cytometry	Screening algorithm
				DBS also showed ≤11 TRECs/µL, the infant was directed for flow cytometry.
Kwan 2014	USA, Mississippi	Program duration 12 months, 37,613 infants were screened.	PerkinElmer Genetics	Dried blood spots were sent to PerkinElmer Genetics, Inc., where the same algorithm as in California was used (40 TRECs/µl initial test, 24 TRECs/µl repeat test), except flow cytometry was not conducted within the screening program, instead by the immunologist at the referral center.
Kwan 2014	USA, Navajo Nation	Program duration 17 months, 3,498 infants were screened.	PerkinElmer Genetics	Dried blood spots were sent to PerkinElmer Genetics, Inc., where the same algorithm as Mississippi was used (40 TRECs/µl initial test, 24 TRECs/µl repeat test).
Kwan 2014	USA, New York	Program duration 24 months, 458,912 infants were screened.	Not reported.	>200 TRECs and RNaseP Cq value <35 considered negative. Abnormal samples retested in duplicate. If average of the 3 samples was >200 or 2/3 tests >200, test considered normal. Borderline category was subsequently added of 124-200 TRECs. Non-premature infants with ≤200 TRECs were referred for diagnostic evaluation.
Kwan 2014	USA, Texas	Program duration 6 months, 183,191 infants were screened.	Not reported.	Initial screen results of <200 TRECs/µL were retested. Final average TRECs ≤150 reported as abnormal or borderline. Samples with undetectable TRECs were immediately referred to an immunologist. All other non-normal results required an additional dried blood spot. Samples with TRECs ≤150 were unsatisfactory and repeat specimens requested.
Kwan 2014	USA, Wisconsin	Program duration 60 months, 340,037 infants were screened.	Not reported.	40/µL whole blood in initial assay for term infants, 25/µL whole blood in initial assay for pre-term infants. 25/µL whole blood in repeat assay for full-term infants and pre-term infants.

Author	Country	Population	Description of TRECs assay and flow cytometry	Screening algorithm
Vogel 2014	USA	Infants in the New York State Newborn Screening Program over a 2 year period from September 29th 2010 to September 28th 2012 485,912 infants were screened.	TREC analysis from DNA extractions from newborn DBS. Multiplex quantitative real-time PCR assay used to detect TREC copy numbers. Follow-up clinical testing included complete blood count (CBC) and flow cytometry studies to assess the number of lymphocytes and T-cells.	>200 TRECs and RNaseP Cq value <35 considered negative. ≤200 TRECs and/or RNaseP Cq value <35 considered abnormal. Samples with RNaseP Cq ≥35 considered assay fails. Borderline category was subsequently added of 124-200 TRECs. Non-premature infants with ≤200 TRECs were referred for diagnostic evaluation. Premature infants with undetectable TRECs were referred for diagnostic evaluation. Abnormal samples retested in duplicate. If average of the 3 samples was >200 or 2/3 tests >200, test considered normal. Samples with average TRECs ≤200 were considered abnormal and referred for follow-up diagnostic and clinical testing. Infants in borderline category were requested a repeat specimen. Premature infants with 200 TRECs were requested a repeat specimen.
Verbsky 2011	USA	Screening included all newborns in the state of Wisconsin from January 1st 2008 until December 31st 2010. 207,696 infants were screened, of which 188,741 (90.87%) were full term and 18,955 (9.13%) were pre-term.	TREC analysis from DNA extractions DBS. RT-qPCR and β-actin performed, followed by flow cytometry for SCID/TCL for positive results. Lymphocyte Subset Analysis by Flow Cytometry. Whole blood stained with antibodies from BD-Immunocytometry System, Beckmann Coulter and Invitrogen. Samples were analysed on a FACSCalibur flow cytometer (Becton Dickinson).	During year 1 of screening, TREC assay cut-off value was 25 TRECs/µl. Cut-off increased to 40 TRECs/µl for the remaining 17 months of screening due to low numbers of abnormal assays. Full term infants with TREC<cutoff and normal B-actin level were considered abnormal and referred to flow cytometry. Those with low B-actin were considered inconcludive and test repeated with new DBS. Pre-term infants (AGA<37 weeks) with an abnormal or inconclusive TREC assay had test repetition until either normal or until infant reached 37 weeks AGA and was reclassified as abnormal.

Table 7 – Characteristics of studies with known retrospective positive samples.

Author	Country	Population	Description of TRECs assay and flow cytometry	Screening algorithm
Adams 2014	UK	Normal Guthrie card samples were compared to known SCID positive Guthrie card samples. Samples were 5081 anonymised normal Guthrie cards and 18 known retrospective SCID positive samples.	Enlite Neonatal TREC kit, Perkin Elmer. Ionazing gate used during punching, Eltex Elektrostatik. Flow cytometry not performed because this was an anonymised study.	TREC cut-off initially set at 40 copies/ µl, then re-evaluated at 35, 30, 25 and 20 copies/ µl. When TREC<cutoff, repeat testing TREC & B-Actin with new punches in Duplicate card from same DBS. B-actin cut off set at 35 copies/ µl. B-actin<cutoff meant invalid result. B-actin>cut off or TREC<cutoff for either duplicate indicated presumptive positive result.
Jilkina 2014	Canada	Manitoba patients diagnosed with severe genetic immune deficiencies (SCID and PID) between 1992 and 2010. Samples were 982 normal controls plus 18 Manitoba patients with known severe genetic immune deficiencies.	DNA extraction by method of New England Newborn Screening Program. TREC assay protocol modified from Comeau et al. No flow cytometry performed.	TRECs value below 252 copies/µl of whole blood was designated screen positive.
Borte 2012	Sweden	Swedish newborns (time frame and size of screening programme not reported), compared with diagnosed SCID samples and other disease control samples. 2560 newborn DBS, 28 known disease samples, including n=18 SCID, and 21 disease control samples.	Triplex PCR method. DNA from a single 3.2-mm punch of the dried blood disks was eluted into Generation DNA Elution Solution (QIAGEN) supplemented with yeast tRNA (Ambion), and subjected to real-time quantitative PCR (RT-qPCR) of TRECs, KRECs, and B-actin (ACTB). Subsequent to gel electrophoresis,	Cutoff set at ACTB≥1000 copies, TRECs≥15/µl and KREC≥10/µl. Inconclusive result when ACTB<1000 copies, TREC<15/µl and KREC<10/µl. Abnormal result when ACTB≥1000 copies and TREC<15/µl and/or KREC<10/µl. Inconclusive and abnormal samples had repeat testing from same Guthrie card.

Author	Country	Population	Description of TRECs assay and flow cytometry	Screening algorithm
			PCR products were purified (MSB Spin PCRapace; Stratec) and sent for direct sequencing.	
Felipe 2016	Spain	Neonates born in 3 hospitals in Seville, Spain, between February 2014 and March 2015. 5160 neonates screened and 7 known PID samples	After DNA extraction from DBS samples and DNA purification (DNA Elution and Purification Solution, Qiagen, Maryland, USA), TRECs, KRECs, and b-actin (ACTB) copy numbers were determined.	TRECs<6/punch, KRECs<4/punch, ACTB>700/punch. Abnormal or inconclusive results (cutoffs not reported) were retested from same DBS; pathologic result (cutoff not reported) in retest had second DBS sample test. In pre-mature infants (gestational age (GA) <37 weeks), heel pricks repeated every 2 weeks until week 37 of corrected gestational age, birth weight ≥2500 g or normality in the assay.
Kanagae 2016	Brasil	Children born at 3 hospitals and 2 clinics; samples from known n=5 SCID and n=2 DiGeorge syndrome were analysed as controls. 8,715 samples out of which 33 were considered inadequate due to inappropriate collection, so 8,682 samples were analysed.	qRT-PCR reaction for TRECs and/or beta-actin; all reagents were purchased from Life Technologies. Flow cytometry consisted of complete blood count and measurement of T, B lymphocytes and NK cells	Cutoff set at <30 TRECS/µl. Samples below cutoff were reanalysed. In second analysis, <30 TRECs/µL and beta-actin >8000/µL abnormal, <30 TRECs/µL and beta-actin <8000/µL inconclusive. Abnormal patients referred to a paediatric immunologist for consultation and confirmatory tests, inconclusive patients had a new sample requested.
Audrain 2015	France	Newborns from one French neonatal screening laboratory were tested between June and October 2012. 5028 newborn DBS and 8 BDS from known SCID patients.	DNA extraction and RT-qPCR were performed as described by Gerstel-Thompson.	Initial cutoff set at <156 TRECs copies/reaction. After all samples tested, mean of all 99th percentiles of each run were calculated to set new cutoffs: >183 TRECs copies/reaction normal, <39 TREC copies/reaction abnormal, 39-183 TREC copies/reaction with RNAseP amplification equivocal and <183 TREC copies/reaction and

Author	Country	Population	Description of TRECs assay and flow cytometry	Screening algorithm
				no RNAseP amplification inconclusive. Samples below cutoff underwent second analysis.
Chien 2015	Taiwan	All newborns screened by the National Taiwan University Hospital Newborn Screening Center, between May 1st 2010 and December 31st 2011 (19 months). These were 106,391 newborns, which covers 35-37% of all newborns in Taiwan.	DNA extracted by Generation DNA Purif, Solution and Generation DNA Elution Solution, QIAGEN. RT-qPCR performed to estimate values for the TREC assay and RNASE P (TaqMan Gene Expression Master Mix, Applied Biosystems). DBS with an abnormal result required a whole blood sampling to perform flow cytometry. For DBS with an abnormal or inconclusive result, TUPLE1 gene copy number analysis for chromosome 22q11.2 microdeletion syndrome was performed.	TREC cut-off <40 TRECs/µl. 0-40 TRECs/µl were defined as inconclusive. DBS with a zero TREC value but a normal RNase P value were defined as abnormal. All inconclusive DBSs required a repeat DBS, and either a low or zero TREC value on the repeat DBS was defined as abnormal.
Kwan 2015	USA	Pilot feasibility study followed by an expanded newborn screening program. Pilot study was 1800 DBS samples. Expanded study was all infants born at Navajo Nation maternity hospitals from February 2012 to June 2012, which screened 6100 infants.	TREC testing of DBS samples (PerkinElmer Genetics, Inc). T-cell lymphophenia by flow cytometry.	TREC cut-off ≥33 TRECs/ µl considered normal. <33 TRECs/ µl had repeat test for TRECs and β-actin copies. Those with low TRECs and normal B-actin were considered positive, and those with low TRECs and low B-actin were considered inconclusive. Inconclusive samples had a repeat DBS
La Marca 2014	Italy	50,000 neonates born in the period January 2011 and June 2012 screened and used to set cu-off values. 4 genetically confirmed early onset and 5 delayed-onset ADA-SCID patients.	TREC testing by tandem mass spectrometry.	25 TRECs/ µl

Author	Country	Population	Description of TRECs assay and flow cytometry	Screening algorithm
Somech 2013	Israel	7 patients diagnosed with SCID from 3 tertiary hospitals, 15 healthy controls	TREC testing by RQPCR. Reactions in the peripheral blood were evaluated using 0.25 ug genomic DNA extracted from the patient's PBMC. Reactions on Guthrie cards determined using 5 ul of extracted DNA. TaqMan universal PCR master mix, specific primers (900nM)and FAM-TAMRA probes.	The findings in age-matched normal individuals were used as control values (>400 TREC copies in 40 samples in which immunodeficiency was ruled out.
Perkin Elmer CONFIDENTIAL	[redacted]	[redacted]	[redacted]	[redacted]

Table 8 – Results from prospective population-based newborn screening program studies using TRECs to detect SCID.

Author	N below TREC cut-off	N test repetition	SCID findings	Incidental findings	Positive predictive value, % (95% CI)	SCID incidence	TCL incidence
Kwan 2014 (Total USA)	Not reported.	Total 1265 referrals to flow cytometry.	Total n=52 SCID cases. 42/52 with typical SCID (N=9 IL2RG, n=6 IL7RA, n=5 ADA, n=4 RAG1, n=3 JAK3, n=1 DCLRE1C, n=1 RAG2, n=1 CD3D, n=1 TC7A, n=1	**N=411** identified infants with non-SCID t-cell Lymphopenia. Of which, ***n=136*** *had a recognised congenital syndrome associated with T-cell impairment* (n=78 DiGeorge, n=21 trisomy 21, n=4 ataxia telangiectasia, n=4 trisomy 18, n=3 CHARGE, n=2 Jacobsen,		1 in 58,000 (reported) (1.72/100,000)	1 in 7,372 (calculated for this review). Based on subgroup analysis for 6 programs defining TCL as T-cell count less

Author	N below TREC cut-off	N test repetition	SCID findings	Incidental findings	Positive predictive value, % (95% CI)	SCID incidence	TCL incidence
			Pallister-Killian, n=6 no mutation found, n=4 genetic testing not completed), 9/52 with leaky SCID (n=4 RAG1, n=2 RMRP, n=1 IL2G, n=1 DCLRE1C, n=2 no mutation found), and 1/52 with Omenn Syndrome.	n=1 CLOVES, n=1 ECC, n=1 Fryns, n=1 Nijmegen breakage, n=1 Noonan, n=1 Rac2 defect, n=1 renpenning, n=1 TAR, n=10 not specified, n=6 cytogenetic abnormalities*).* ***n=117*** *secondary T-cell impairment* (n= 30 cardiac anomalies, n=23 multiple congenital anomalies, n=15 loss into third space, n=15 gastrointestinal anomalies, n=4 neonatal leukaemia, n=30 not specified) ***n=29*** *preterm birth alone*, ***n=12*** *variant SCID,* ***n=117*** *unspecified T-cell lymphopenia*.			than 1500/ul: PPV 36% (32%-41%) for a nonnormal TREC test to indicate TCL.
Kwan 2014 (California)	Not reported.	N=206 referrals to flow cytometry.	N=23	n=57*	Not reported	1 in 60,000 (1.7/100,000)	Non-SCID TCL 1 in 32,000 (3.1/100,000)

Author	N below TREC cut-off	N test repetition	SCID findings	Incidental findings	Positive predictive value, % (95% CI)	SCID incidence	TCL incidence
Kwan 2014 (Colorado)	Not reported.	N= 10 referrals to flow cytometry.	N=1	n=3*	Not reported	1 in 71,000 (1.4/100,000)	Non-SCID TCL 1 in 26,000 (4.2/100,000)
Kwan 2014 (Connecticut)	Not reported.	N=22 referrals to flow cytometry.	N=3	n=6*	Not reported	1 in 19,000 (5.2/100,000)	Non-SCID TCL 1 in 11,000 (8.8/100,000)
Kwan 2014 (Delaware)	Not reported.	N=9 referrals to flow cytometry.	N=1	n=3*	Not reported	1 in 11,000 (8.9/100,000)	Non-SCID TCL 1 in 3,700 (26/100,000)
Kwan 2014 (Massachusetts)	Not reported.	N=63 referrals to flow cytometry.	N=4	n=47*	Not reported	1 in 73,000 (1.4/100,000)	Non-SCID TCL 1 in 6,400 (16/100,000)
Kwan 2014 (Michigan)	Not reported.	N=114 referrals to flow cytometry.	N=2	n=76*	Not reported	1 in 81,000 (1.2/100,000)	Non-SCID TCL 1 in 2,100 (47/100,000)
Kwan 2014 (Mississippi)	Not reported.	N=5 referrals to flow cytometry.	N=1	n=4*	Not reported	1 in 38,000 (2.7/100,000)	Non-SCID TCL 1 in 13,000 (8.0/100,000)
Kwan 2014 (Navajo Nation)	Not reported.	N=1 referral to flow cytometry.	N=1	n=0*	Not reported	1 in 3,500 (29/100,000)	Non-SCID TCL 1 in 3,500 (29/100,000)
Kwan 2014 (New York)	Not reported.	N=478 referrals to flow cytometry.	N=10	n=88*	Not reported	1 in 49,000 (2.0/100,000)	Non-SCID TCL 1 in 6,600 (15/100,000)
Kwan 2014 (Texas)	Not reported.	N=249 referrals to flow	N=2	n=80*	Not reported	1 in 92,000 (1.1/100,000)	Non-SCID TCL 1 in 2,600 (39/100,000)

Author	N below TREC cut-off	N test repetition	SCID findings	Incidental findings	Positive predictive value, % (95% CI)	SCID incidence	TCL incidence
		cytometry.					
Kwan 2014 (Wisconsin)	Not reported.	N=108 referrals to flow cytometry.	N=4	n=45*	Not reported	1 in 85,000 (1.2/100,000)	Non-SCID TCL 1 in 8,100 (12/100,000)
Vogel 2014	0.36 % (1 in 278) abnormal results.	N=1307 had repeat DBS (561 premature and 746 non-premature). N=531 referred for a diagnostic evaluation. Addition of the borderline category reduced the overall referral rate from 0.2 to 0.1 %.	N=9 typical SCID (n=1 IL7R, n=3 IL2RG, n=2 ADA, n=3 unknown). N=1 = leaky SCID (IL2RG).	N=30 idiopathic T-cell lymphopenia (including N=18 22q11 deletion), n=27 non-SCID syndrome with T-cell impairment, n=17 secondary T-cell lymphopenia, n=13 other laboratory abnormalities.	Typical and leaky SCID: 2.1% (0.6 % before and 2.7 % after addition of the borderline category). Overall: 20.3% (11.0% before and 24.0 % after addition of the borderline category).	1 in 48,500	1 in 5,000
Verbsky 2011	Pre-term infants: n=94 (0.045%) abnormal and n=241 (0.116%) inconclusive.	N=449 retests N=292 repeat DBS. N=72 referrals. Total repeat testing rate	N=4 SCID (n=1 ADA, n=1 T-B-NK+, n=2 T-B+NK+).	N= 14 primary TCL, (n=5 reversible TCL, n=4 22q11.2 deletion syndrome, n=5 SCID/severe TCL, n=1 clinically detected 22q11.2 deletion	45.83 (34.3-57.3)	Not reported	Not reported

Author	N below TREC cut-off	N test repetition	SCID findings	Incidental findings	Positive predictive value, % (95% CI)	SCID incidence	TCL incidence
	Full-term infants: n=63 (0.030%) abnormal and n=51 (0.025%) inconclusive.	0.19%. 33/72 abnormal results had TCL.		syndrome). n=1 RAC2. n=19 (58%) secondary TCL.			
Kwan 2013	N=879 required action. 34/879 referred directly to flow cytometry (urgent positive samples). 39/879 referred directly to flow cytometry (initial positive samples).	806/879 repeat TREC test. Total n=161 underwent flow cytometry, representing 1 in 6200 births.	n=11 SCID (n=4 IL2RG, n=1 JAK 3, n=3 IL7R, n=2 RAG1, n=1 unknown).	N=1 DiGeorge syndrome (22q11 deletion), n=3 leaky SCID or Omenn syndrome (n=2 RAG1, n=1 RMRP). n=6 had a variant of SCID/CID. n=50 (31%) had T-cell lymphopenia. N=29 non-SCID TCL secondary to clinical syndromes, congenital malformations, or other nonimmune conditions (excluding preterm birth alone).	Not reported	Typical SCID 1 in 90,000. Leaky SCID 1 in 331,000. Variant SCID 1 in 166,000. Typical SCID, leaky SCID, and variant SCID had a combined incidence of 1 in 49,700 births.	1 in 19,900

*Incidental findings Ns taken from van der Spek 2015

Table 9 – Results from studies with known retrospective samples.

Author	N below TREC cut-off	N test repetition	SCID findings	Incidental findings

Author	N below TREC cut-off	N test repetition	SCID findings	Incidental findings
Kanegae 2016	n=4 (0.05%) abnormal after requantification. If initial cut-off set at <26 TRECs/µl, 0.43% (37 samples) requantified and 0.03% (3 samples) abnormal.	n=49 (0.56%) requantified. N=3 referred to flow cytometry, n=1 lost to follow-up.	n=3 flow cytometry results not reported. All known SCID samples (5/5) were detected.	All known DiGeorge samples (2/2) were detected.
Felipe 2016	N=109 low copies of ACTB.	N=39 (0.6%) insufficient material to repeat test. N=77 (1.5%) repunched. N=10 (0.19%) positive results were re-called, out of which n=5 had subsequently normal results and n=5 (0.1%) were confirmed positives.	0/5 positives had SCID 4/4 known SCID samples detected.	1/5 died before diagnosis. 2/5 extreme preterm and are under follow-up. 2/5 infants' mothers receiving immunosuppressive treatment including azathioprine during pregnancy. Samples from known PIDs correctly detected, including n=2 XLA and n=1 AT.
Chien 2015	n=5 abnormal. n= 432 (0.4%) inconclusive. n=19 had abnormal after repeat test.	n=0 retests. n=432 (0.41%) repeat DBS. N=24 (0.02%) referred.	n=2 SCID (n=1 IL2RG, n=1 RAG1). Another n=2 SCID in unscreened sample; showed	n=16 other TCL. n=2 idiopathic T-cell lymphopenia (molecular defects not

Author	N below TREC cut-off	N test repetition	SCID findings	Incidental findings
			zero TRECs in first DBS.	identified), n=5 22q11.2 microdeletion syndrome, n=9 other medical conditions.
Kwan 2015	Pilot study: n= 1787 (99.3%) normal TRECs. n=11 inconclusive. Expanded study: n=0 inconclusive. N=4 undetectable.	Pilot study: N=11 repeat DBS.	Pilot study: N=0 SCID Expanded study: N=4 SCID (4/4 SCID-A)	Pilot study: n=1 low TRECs and TCL associated with congenital anomalies. N=1 refused further testing. Expanded study: N/R
Audrain 2014	TREC > 183 copies/reaction: n=0 abnormal, n=54 equivocal and n=78 inconclusive. TREC >100 copies/reaction: n=0 abnormal, n=4 equivocal and n=55 inconclusive.	TREC > 183 copies/reaction: n=132 (2.62%) retested. n=0 abnormal n=9 equivocal n=2 inconclusive. TREC >100 copies/reaction: 0.04% retested. n=0 abnormal n=2 equivocal n=0 inconclusive.	None. Using TREC>183 copies/reaction cutoff: 7/8 known SCID samples had undetectable TRECs, 1/8 had equivocal TRECs. Using TREC>100 copies/reaction cutoff: 7/8 known SCID samples were identified, 1/8 was missed.	Not reported.

Author	N below TREC cut-off	N test repetition	SCID findings	Incidental findings
Borte 2012	N=2538 normal. N=16 abnormal N=6 inconclusive.	N=22 retested. N= 6 abnormal N=1 inconclusive N=15 normal.	Not reported.	Not reported.
La Marca 2014	Positive rate at the first screening test was 0.02% (10:50,000 live births).	9/10 normalised at the second tier test.	All truly positive ADA-SCID samples confirmed.	Not reported
Somech 2013	No normal control neonates had TREC below the cut-off value for diagnosing SCID.	Not reported.	All seven SCID patients had values beyond the test range for SCID.	Not reported
Adams 2014	N=51 (1%) identified as presumptive positives using the initial TRECs cut-off of 40 copies/µl; equates to 7000 presumptive positives per year TRECs cutoff of 35 copies/µl equates to 2100 presumptive positives. TRECs cutoff of 30 copies/µl equates to 840 presumptive positives. TRECs cutoff of 25 copies/µl equates to 560 presumptive positives. TRECs cutoff of 20 copies/µl equates to 280 presumptive positives and would still detect all SCID samples included in the study.	No repeat runs were required due to assay failure. N=209 (4.1%) required a repeat test. N=2 had repeat DBS. N=53 referrals. If extrapolated to the UK population (~700,000 newborns per year), this would mean an extra 138 repeat heel pricks.	n=4 ADA, n=2 Gamma-chain, n=2 RAG deficient, n=1 PNP and n=7 undefined SCID.	n=2 Omenn's SCID
Jilkina 2014	n=19 screen positives (9/19 from known SCID/PID patients and 10/19 newborn infants).	Not reported.	n=7 screen positives from known SCID	n=2 screen positives from known PID

	9/18 known SCID/PID patients were not identified by TREC assay. 100% of T-cell-deficient forms of SCID and PID were identified. 2/8 SCID and 1/4 PID T-cell-positive forms were identified.		patients (3 ADA, 1 CD3δ def, 1 clinical SCID, 2 ZAP 70 deficiency). N=6 screen negatives (3 ZAP70 def, 3 IKKβ def) .	patients (1 CHH, 1 CID). N=3 Screen negative PIDs (1 CID, 1 WAS, 1 XLP).
Perkin Elmer CONFIDENTIAL	[redacted]	[redacted]	[redacted]	[redacted]

Table 11 – Incidence and screening positive predictive values calculated and reported by van der Spek et al. (2015).

Study reference	Country	Incidence SCID/100,000	Incidence TCL/100,000	SCID PPV, % (95% CI)	TCL PPV, % (95% CI)
Chien 2015	Taiwan	1.9	16.9	8.3 (-2.7-19.4)	75.0 (57.7–92.3)
Kwan 2014	California	1.7	5.8	11.2 (6.9-15.5)	38.8 (32.2–45.5)
	Colorado	1.4	5.6	10.0 (-8.6-28.6)	40.0 (9.6–70.4)
	Connecticut	5.3	15.8	13.6 (-0.7-28.0)	40.9 (20.4–61.5)
	Delaware	8.9	35.7	11.1 (-9.4-31.6)	44.4 (12.0–76.9)
	Massachusetts	1.4	17.4	6.3 (0.3-12.4)	81.0 (71.3–90.6)
	Michigan	1.2	48	1.8 (-0.7-4.2)	68.4 (59.9–77.0)
	Mississippi	2.7	13.3	20.0 (-15.1-55.1)	100
	Navajo Nation	28.6	28.6	100	100
	New York	1.9	20	1.7 (0.6-2.8)	18.3 (15.0–21.6)
	Texas	1.1	44.8	0.8 (-0.3-1.9)	32.9 (27.1–38.8)
	Wisconsin	1.2	14.4	3.7 (1.0-7.3)	45.4 (36.0–54.8)
Vogel 2014	USA	1.9	20	1.7(0.6–2.8)	18.3 (15.0–21.6)
Kwan 2013	USA	1.2	5	7.5 (3.4-11.5)	31.1 (23.9–38.2)
Verbsky 2011	USA	1	15.9	2.8(−1.0–6.6)	45.8 (34.3–57.3)

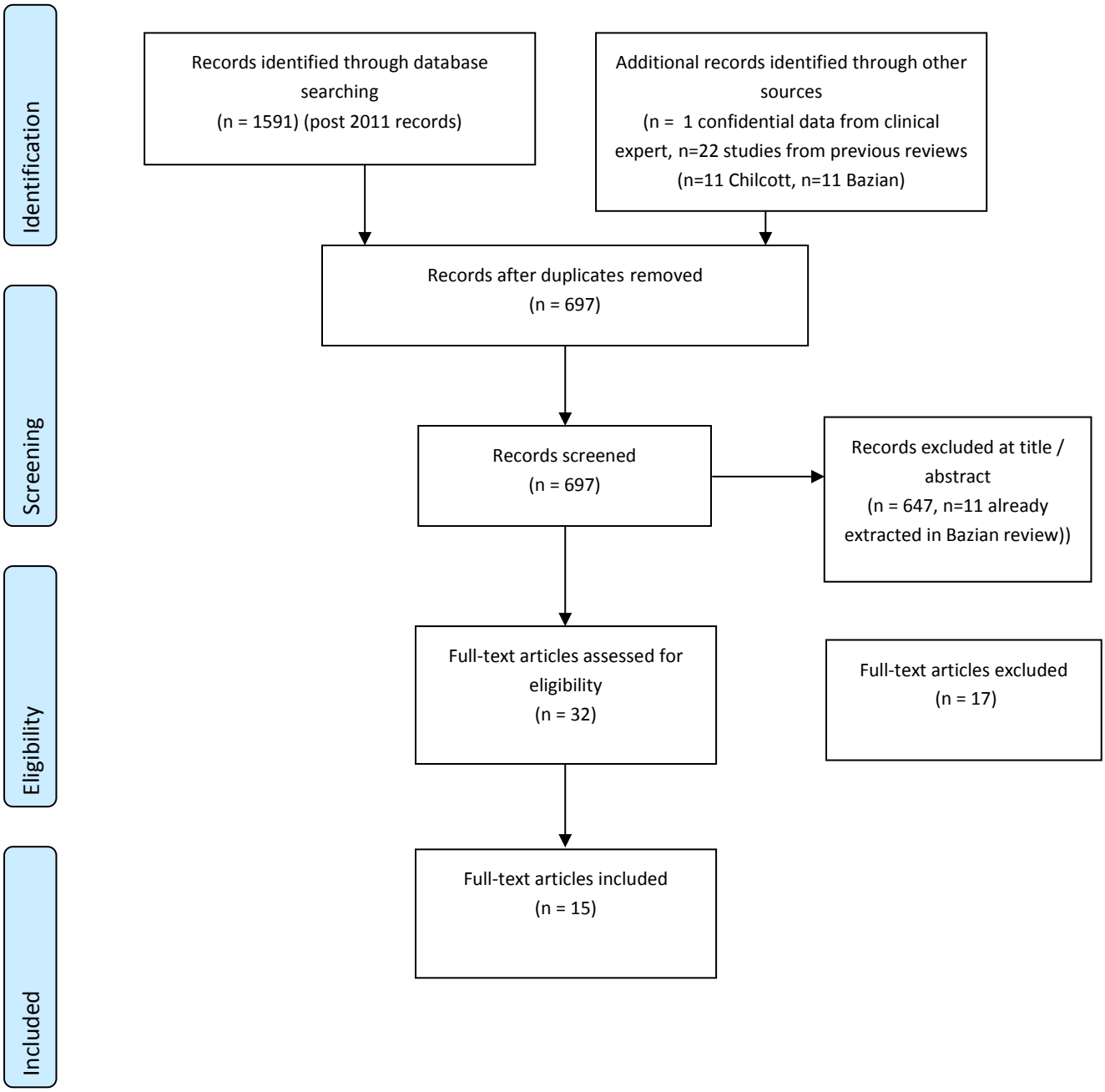


Figure 4. PRISMA Flow Diagram: Newborn TREC Screening for SCID

4.3 Key question 3 (Early vs. late treatment)

Does early hematopoietic stem cell transplantation (HSCT) lead to improved outcomes compared with late HSCT in SCID patients?

This relates to NSC criterion 9 and 10:

9: 'There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.'

10: There should be agreed evidence based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.

4.3.1 Description of the evidence

Figure 23 shows the PRISMA flow diagram for the SCID natural history with treatment review. Electronic searches identified 3696 records after de-duplication, of which 1526 were post 2011 and therefore sifted. 72 full text records were assessed, of which 64 papers were subsequently excluded for not meeting inclusion / exclusion criteria. 22 papers met the inclusion criteria of HSCT and were included in the narrative synthesis. Of these, 17 were identified in the Chilcott 2016 review and 8 from the updated search. 22 studies reported HSCT, however 2 gene therapy studies were identified, and 1 study comparing gene therapy to HSCT. The latter studies were included for completeness and will be described separately.

4.3.2 Characteristics of included studies

Of the 22 identified HSCT studies, most were retrospective chart reviews, following cohorts of SCID patients who were treated at a single centre (Baffelli 2015, Cipe 2012, Cuvelier 2016, Giri 1994, Neven 2009, Mazzorali 2007, Myers 2002, Neven 2009, Patel 2008, Patel 2009, Dell Railey 2009, Rogers 2001, Sarzotti-Kelsoe 2009, Slatter 2008, Titman 2008, Wahlstrom 2016). Teigland 2013 followed-up patients from one institution who underwent repeat transplant with either the same or a different donor. A minority of studies reported data from multiple centres (Bertrand 1999 reports data from 18 centres, Brown 2011 reports data from 2 centres, Gennery 2010 reports data from 37 centres, Honig 2007 data is from 2 centres, Pai 2014 data is from 25 centres). Chan 2011 directly surveyed families who had a family member with SCID or Omenn Syndrome.

Descriptions of the reason for diagnosis of SCID in patients was not comprehensive across studies, however of those studies where this was described, most diagnoses were a mix of patients identified through family history (e.g. siblings with diagnosed SCID), and those identified through failure to thrive, recurrent infections, respiratory pneumonia or bronchiolitis (Cipe 2012, Giri 1994, Honig 2007, Neven 2009). Brown 2011 directly compared two cohorts of patients defined by diagnosis, with a sibling cohort and a proband cohort (patient being the first diagnosed within the family). Patients receiving treatment in the study reported by Myers 2002 were all diagnosed due to family history, with diagnosis both in utero or at birth. Study Ns ranged from 11 (Giri 1994, Rogers 2001), to 1,482 – of which 699n SCID, 783 non-SCID (Gennery 2010). Baffelli 2015 studied 27 patients with ADA deficiency. These patients included one neonate identified during pregnancy.

Age at diagnosis: Median age at diagnosis was reported in many studies, with some studies reporting median age of onset of symptoms. Chan 2011 reported a median age at onset of symptoms of 8 weeks, diagnosis of SCID at 28 weeks, and treatment initiated at 28 weeks. In the Cipe study, median age at diagnosis was 4 months. Median age at diagnosis in Giri 1994 was 8 months. In Pai 2014, patients were diagnosed at median 138 days. Age at diagnosis in Teigland 2008 ranged from 0 days to 1.7 years. In the Myers 2002 study, where all diagnoses were early due to known family history, median age at transplant was 10 days. In Neven 2009, 39% of patients were diagnosed at 3 months or earlier, and 61% diagnosed at later than 3 months. Brown 2011 compared outcomes after transplant for sibling and proband cohorts. Of the sibling cohort, 4 patients were diagnosed antenatally. The median age for those without antenatal diagnosis was 0 days (range 0-29 days). This compared to the proband cohort, where median age at diagnosis was 143.5 days (range 1-455 days). Myers 2002 also compared early versus late transplant, with diagnosis made due to known family history in 21 patients, 9 of which were diagnosed in utero, and 12 diagnosed at birth. Age at diagnosis was not reported in the late transplant group. Cuvelier 2016 report a median age at diagnosis of 13 months (range 12 days to 27 months).

Age at transplant: Most studies reported age at transplant, with some studies specifically comparing early versus late transplant. The oldest mean age at transplant was reported by Titman 2008, at 3 years 6 months. Patel 2008 reported earlier median transplant age for matched donor transplants (1.8 months) compared to mis-matched donor transplants (6.5 months). Giri 1994 reported transplants performed at median 13 months. HSCT transplant was performed at ages between 2 months and 2.5 years in the study by Honig 2007, and 180 days in Pai 2014. Mean age at transplant

for ADA-SCID patients in Rogers 2001 study was 9 months. The large multi-centre study reported by Gennery 2010, median age at transplant was reported by time period of transplant (pre 1995, 1995-1999, 2000-2005) and by match of donor (genotypical HLA identical, phenotypical HLA identical, HLA mismatched, or unrelated). Median age for all groups is shown in table x., however typically unrelated donor transplants were performed at a later age. In Chan 2011, transplants were performed at a median age of 28 weeks. Brown 2011 do not provide specific data on age at transplant, however proband versus sibling cohorts were compared as a proxy for 'early versus late' transplant. In Bertrand 1999 median age at transplant was 7 months for B+ SCID and 6.5 months for B-SCID. Myers 2002 compared early (first 28 days of life) versus late (after 28 days of life) transplant groups, with median age of early group 10 days, and for the late group 190 days. In Neven 2009, 25% of patients received transplant at less than 3 months, with the remaining 75% receiving transplant at >3.5 months. In Wahlstrom 2016, median age at transplant was 139 days. Baffelli 2015 and Cuvelier 2016 only report patient level data.

Treatments were all HSCT. Most studies contained a mix of patients who had received transplants from either matched/unmatched and related/unrelated donors. In Bertrand 1999, Giri 1994, Myers 2002, Patel 2008, and Dell Railey 2009 all donors and recipients were related. A range of conditioning regimen and post-transplant GvHD prophylaxis were reported. These varied both between treatment centres, and within centres dependent on individual patient need. Conditioning regimens are detailed for each study in the tables below. Duration of follow-up within the studies varied greatly. Follow-up in Bertrand 1999 ranged from 6 months to 14 years, Cipe 2012 the range was 4 to 74 months; Gennery 2010 follow-up ranged from 1 year to 9.6 years; Honig 2007 ranged from 3 years 11 months to 22 years and 2 months; Patel 2008 follow-up range was patient age 10 to 18 years; Dell Railey follow-up duration ranged between 6 months and 26 years post-transplant, and Titman (2008) ranged between 13 months and 25 years. Neven 2009 reported follow-up duration between 2 and 34 years after HSCT; Teigland 2013 reported follow-up of up to 28 years, whilst Wahlstrom reported a median follow-up of 7 years, with a range of 2 months to 25 years. Pai followed patients at a range of set intervals from 100 days to 10 years post-transplant. Slatter followed patients up at 2 years survival. Mazzolari 2007 followed up patients 5 years post-transplant, with Baffelli 2015 reporting their longest follow-up time as 15 years. The median follow-up in Cuvelier 2016 was 13.5 years, ranging from 1.9 to 24 years.

4.3.3 Analysis of the evidence

Survival: Most studies reported survival at follow-up as the main outcome. Survival rates were reported as survival at follow-up in some studies, in which case this varied, or as 3 year survival percentages (Gennery 2010), 8 year survival (Dell Railey 2009), 5 year survival (Pai 2014). Slatter 2007 reported 2 year survival. A minority of studies reported survival before transplant. Chan 2011 report 20% of infants died after diagnosis but without receiving definitive treatment. Brown 2011 report 35.4% of the proband cohort dies before HSCT, where only 1 out of 60 of the sibling cohort died before HSCT. All deaths were caused by infectious complications. Giri 1994 report 6/8 patients with lung infection died before transplant, and 0/5 patients with infection the week before transplant survived. A range of overall survival rates after transplant were reported across studies, from 46% (Giri1994), 72.4% (Mazzorali 2007), 66% (Cipe 2012), 74% (Pai 2014), 75% (Teigland 2013), 80% (Wahlstrom 2016), 100% (Cuvelier 2016). A number of factors were shown to influence survival including age at transplant (Bertrand 1999, Pai 2014, Dell Railey 2009); time period of transplant (Bertrand 1999, Gennery 2010); sibling/proband cohort (10% mortality versus 60% mortality) (Brown 2011); donor matching (Gennery 2010, Honig 2007); and history of infection (Pai 2014).

Early versus late transplant survival: Dell Railey 2009 report 96% survival for the early group versus 70% for the late group (8-year Kaplan-Meier survival). Chan 2011 report that those who received treatment and survived were mean 29 weeks of age at transplant, whilst those who received treatment and died were mean 57 weeks of age at transplant. Brown 2011 report a significant improvement in outcome in a subcohort analysis of SCID patients who were diagnosed at birth (93% survival) compared to the proband group (54% survival). Bertrand 1999 report 73% survival for patients receiving transplant at <6 months compared to 54% survival for >6 months for B+SCID patients. The impact on survival for B-SCID patients was not significant. Myers 2002 report 95% survival for the group of patients transplanted early versus 74% survival for those transplanted late. Pai 2014 report early transplant at 3.5 months or younger resulted in 94% 5 year survival, compared to 90% 5 year survival in >3.5 month age, for patients with no history of infection. Those with active infection at time of transplant had 50% 5 year survival, and those who had resolved infection had 82% 5 year survival. Teigland 2013 report an average age at transplant of 194 days for patients still alive, compared with 273 days for those who had died.

Other long-term outcomes: Some studies report further outcomes including complications, cognitive, behavioural and neurological health and development. Honig 2007 report 50% of transplant survivors have no clinical complications, although 50% have significant neurologic and cognitive

defects. Rogers 2001 report the ADA-SCID group fell into the abnormal range for total behaviour checklists and hyperactivity. Brown 2011 report 10/57 of the sibling cohort had a total of 12 infections, whilst the proband cohort 25/29 had multiple infections. Slatter reported incidence of plantar warts and single invasive infection after 2 years. Titman 2008 report a lower mean IQ in transplant survivors than the general population, and that 19% fell into the learning disabilities range of ability. The mean score on Conner's Rating Scale indicated children had higher levels of difficulties with concentration, attention and hyperactivity at follow-up than the general population. Dell Railey 2009 reports the prevalence of a number of health issues at follow-up, including receiving standing antibiotics (27%), asthma (14%), sinusitis (20%), development delay (10%), ADHD (21%), cerebral palsy (2%), skin rashes (25%), HPV infection (12%), with 3% requiring special schooling. However most patients were considered healthy by their families at follow-up (85%). 22% had received booster transplants. Neven 2009 also reports a range of clinical events 2 years after transplant, including persistent cGVHD (11%); autoimmune/inflammatory events (13%); severe or recurrent infection (12%); chronic HPV infection (25%); nutritional support (20%); and 12% required a booster transplant. Mazzolari 2007 report long-term clinical and immunological deficiencies (5 years post-transplant), including 17.5% with growth insufficiencies, 12.5% with low stature, 17.5% with endocrine abnormalities, 10% with severe neurologic problems, and 12.5% with significant infections. Table X describes other reported outcomes by study.

Studies of gene therapy. 2 peer-reviewed published studies were identified that reported outcomes after gene therapy treatment for SCID. Cicalese (2016, Italy), a long-term follow-up study of Aiuti 2009), studied 18 patients with ADA-SCID for whom an HLA-identical match was not available. Patients received gene-transduced autologous CD34+ cells. Hacein-Bey-Abina 2014 report data from 9 patients in France, the UK and the USA with SCID-X1, who received SIN γ-retrovirus gene therapy due to a lack of appropriate donor or who had an active, therapy-resistant infection. Neither study reported age at diagnosis, however treatment was received at median age 1.7 years (range 0.5 to 6.1 years) in the Cicalese study, and median age 8.0 months in the Hacein-Bey-Abina study. Cicalese 2016 report 100% survival over 2.3 to 13.4 years follow-up, whilst Hacein-Bey-Abina 2014 report a survival rate of 8 out of 9 patients at follow-up, with one child deceased. No statistical analyses were performed to explore the effect of early versus late treatment. 15 out of 18 children did not require further intervention. Other complications were reported by Cicalese 2016. The most common reported complications after treatment were infections (62%), although the rate of infections dropped from 1.17 events per person-year pre-treatment to 0.17 events after treatment. 12 out of 14 children were attending pre-school or school at follow-up. Little follow-up data in addition to

survival was reported by Hacein-Bey-Abina, however they report that 7 out 9 infections resolved after gene therapy.

Studies comparing HSCT to gene therapy. One study was identified that compared HSCT to gene therapy. Touzot 2015 reported data from 13 patients who had undergone HSCT and compared then to 14 patients who had undergone gene therapy at a single centre in France. All patients had SCID-X1, and those that had received gene therapy are also reported in other studies (Hacein-Bey-Abina 2014, and Bazian 2012). 2 patients in each group died after treatment. Resolution of disseminated infection was fastest in the gene therapy group (median 11 months compared to median 25.5 months in the HSCT group).

Methodological quality of included studies

Methodological quality of studies was assessed using an adapted version of the CASP checklist for cohort studies. Results of the quality assessment can be found in appendix 2. Studies were mainly retrospective reviews of medical records. In most studies, all patients were followed-up. In 2 studies a small proportion of patients could not be followed-up. Length of follow-up varied between studies, with some studies reporting follow-up of greater than 25 years. However it was not possible to distinguish mean/median follow-up times in some studies and it is expected that there was wide variation. Studies mostly described treatment protocols in depth, including conditioning regimens. Confounders were identified in the majority of studies, the most common of these were age at transplant, infections, and matched/mismatched donor status. Consistency of results compared to other studies was good, with a few exceptions, for example Titman 2008 whose small study found that age at transplant was not related to cognitive outcome.

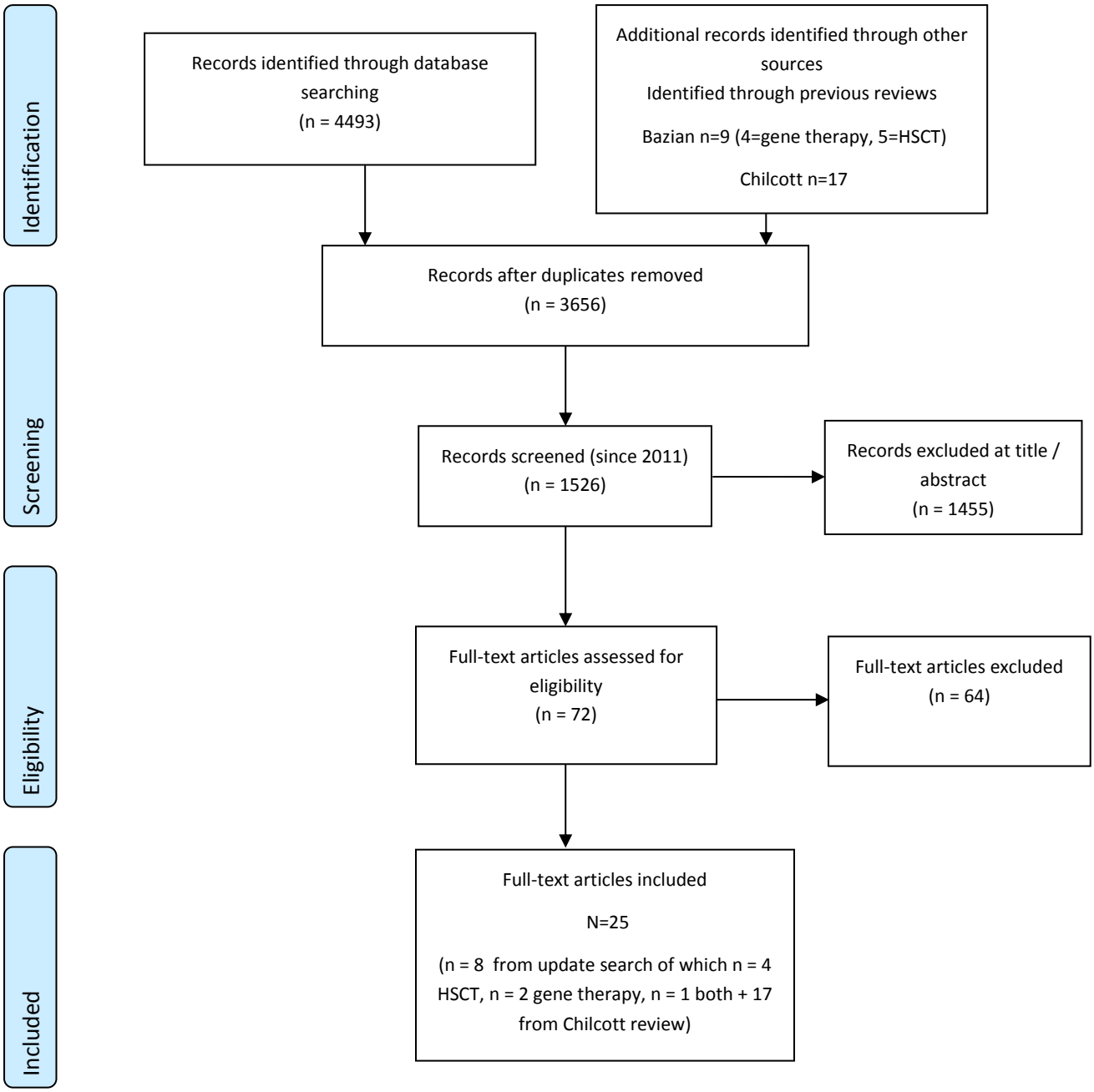


Figure 5. PRISMA Flow Diagram: Early vs. late treatment

4.3.4 Discussion: Question 3

Twenty five studies were identified that met the inclusion criteria for the review. 22 of these were studies of HSCT for SCID patients, two were of gene therapy and one compared HSCT to gene therapy. The evidence show that HSCT is an effective treatment for SCID patients. A number of factors were shown to influence its effectiveness, including matched-related donors and history of infections. Early transplant has been consistently shown to improve survival outcomes. This was demonstrated in a number of studies, where early diagnosis was made due to family history of SCID, and also in studies that statistically analysed the effect of age at transplant on survival. In particular HSCT is more effective when performed at an early age, and before the onset of infections, or, after any prior infection is resolved. The prevalence of long-term complications or adverse outcomes was less consistently reported. Studies that did report these suggest that long-term outcomes such as invasive infections, HPV infection, asthma, or sinusitis are not uncommon. There is some evidence of developmental delay or ADHD. Repeat transplants may be necessary, and there may be an increased need for continued antibiotic use. However evidence relating to these types of outcomes is not widely reported. Where general health perceptions were measured, patients were considered by parents to be healthy.

In the last external review of Screening for SCID for the UK National Screening Committee (Bazian 2012), criterion 10 ('there is an effective treatment with evidence that early treatment improves prognosis') was met. Evidence published since this last review further supports this conclusion, and offers further evidence for the conditions under which HSCT may be more or less effective. Criterion 9 requires that 'there should be agreed evidence based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.' The Bazian review considered this criterion as 'met', based on the poor prognosis of children with SCID without treatment. The review cites existing standard of care guidelines issued by the UK Primary Immunodeficiencies Network, and guidelines for the treatment of PIDs, including SCID, with HSCT outlined by the European Group for Blood and Marrow Transplantation and European Society for Immunodeficiencies. However, at the time of the review, guidelines for the treatment of patients with low TREC counts but without typical SCID were unclear.

Table summaries for SCID treatment (Objective 3)

Table 12 – Study characteristics of SCID treatment studies - HSCT.

Study reference	Country	Study design	Participants	N	Time-frame	Follow-up
Dell Railey 2009	USA	Cohort study, consecutive patients.	Patients with SCID who received bone marrow transplants at one centre. Follow-up of 124 survivors.	N=124 survivors of 161 transplanted patients. N=111 responded to follow-up questionnaire.	May 19, 1982 to August 15, 2008.	Follow-up range 6 months to 26 years post-transplant (median 8.7 years). Median follow-up time 9.2 years (25th percentile, 5.0 years; 75th percentile, 13.4 years) for patients who received their transplants in the first 3.5 months of life, compared with 8.5 years (25th percentile, 2.3 years; 75th percentile, 14.9 years) for patients who were transplanted after 3.5 months of age.
Sarzotti-Kelsoe 2009*	USA	Cohort study, consecutive patients.	All 123 survivors from a total of 158 SCID infants transplanted initially at Duke University Medical Center (DUMC), 2 more transplanted elsewhere but given booster transplantations at DUMC and 3 transplanted elsewhere but followed longitudinally at DUMC	N=128.	May 19, 1982 to December 31, 2007.	Patients ranged from 6 months to 25.6 years after transplantation, with 68 of them being more than 10 years after transplantation.
Patel 2008	USA	Retrospective cohort study.	Patients with SCID who underwent bone marrow transplantation at one centre.	N=25.	1981 to 1995.	Age at last follow-up range 10 to 18 years.
Patel 2009	USA	Retrospective cohort study	Patients with SCID undergoing HSCT at one centre	N=23	1998 to 2007	Median follow-up differed by outcome. Median survival follow-up for MRD was 7.5 years (range 1.5 to 9.5 years); MMRD was 4.3 years (range 1.8 to 8 years); MUD was 2 years (range 1.8 to 7 years).

Study reference	Country	Study design	Participants	N	Time-frame	Follow-up
Gennery 2010	Europe	Retrospective cohort study.	Patient data collected from the SCETIDE registry – 37 centres holding data on children undergoing HSCT for SCID or PID.	37 European centres, n=699 patients with SCID and n=783 non-SCID.	1968 to December 31, 2005. Division into 3 time periods: pre-1995, 1995-1999 and 2000-2005	Median follow-up for SCID patients (years): <1995: genotypical HLA identical 8.8, phenotypical HLA identical 9.6, HLA mismatched 9.3, Unrelated donor 8.9. 1995-1999: genotypical HLA identical 2.0, phenotypical HLA identical 2.5, HLA mismatched 4.5, Unrelated donor 7.1. 2000-2005: genotypical HLA identical 1.0, phenotypical HLA identical 1.2, HLA mismatched 1.4, Unrelated donor 1.8.
Chan 2011	USA	Retrospective survey.	Families identified themselves as having a member affected with SCID or Omenn Syndrome. Survey sent retrospectively to families on Immune Deficiency Foundation database or subscribers to SCID Angels for Life Foundation.	N=126 families with N=158 SCID cases.	January 13 through 30 of 2009.	N/R
Brown 2011	UK	Retrospective cohort study.	Two cohorts of SCID patients from 2 UK centres: sibling cohort (SCID diagnosis made antenatally) or at birth because of family history, compared with proband cohort (first presenting person in family).	Sibling cohort n=60, proband cohort n=48.	1982-2010 (sibling cohort) and 1979-2009 (proband cohort).	N/R
Bertrand 1999	Europe	Retrospective cohort study.	Patients with B- or B+ SCID in 18 centres in Europe undergoing BMT.	N (total) = 178, N (B+ SCID) =122 and N (B-SCID) =56	1981 to 1995.	Minimum follow-up 6 months, maximum follow-up 14 years. Median follow-up 57 months for B+ SCID, 52 months for B- SCID.
Giri 1994	Australia	Retrospective	Patients with primary	N=11, of which	April 1985 to	Minimum follow-up 6 months.

Study reference	Country	Study design	Participants	N	Time-frame	Follow-up
	and New Zealand	cohort study.	immunodeficiency disorders receiving bone marrow transplantation from one institution.	n=9 SCID; n=1 MHC, n=1 Wiscott Aldrich Syndrome.	May 1992.	
Honig 2007	Germany	Cohort study.	Patients with ADA-SCID treated with HSCT at 2 centres.	N=15.	Since 1982.	Age at follow-up range 3 years 11 months to 22 years 2 months.
Mazzorali 2007	Italy	Retrospective cohort study.	Consecutive children with severe T-cell immunodeficiency who received HSCT at one centre .	N=58.	March 1, 1991 to June 30, 2002.	5 years post-transplant.
Myers 2002	USA	Retrospective/ prospective study.	Infants with SCID receiving bone marrow transplants in the first 28 days of life at one centre during 19.2 year period. Results compared with 70 infants who had successfully received transplants after 28 days.	n=21 <28 days, n=70 retrospective analysis of successful transplants >28 days.	Cases during the past 19.2 years.	Follow-up up to 19 years.
Cipe 2012	Turkey	Retrospective cohort study.	Infants with primary immunodeficiency diseases who underwent haploidentical transplantation.	N=18, undergoing 30 transplantations.	July 2000 to December 2010.	Follow-up months after HSCT range 4-74.
Pai 2014	USA	Retrospective cohort study.	Infants with classic SCID who had received hematopoietic-cell transplants at 25 PIDTC centres.	N=240.	January 1, 2000 to December 31, 2009.	Follow-up at 100 days, 6 months, and 1, 2 to 5, and 6 to 10 years post-transplant.
Neven 2009	France	Retrospective cohort study.	Individuals with SCID who had received allogeneic HSCT in one centre and were alive 2 years later.	N=90.	1972 to 2004.	Median follow-up period 14 years after HSCT (range 2-34 years).
Rogers 2001	UK	Cohort study.	Patients with ADA-SCID who were under follow-up after bone marrow transplantation at one centre.	N=11 patients with ADA-SCID (o/o 13 who underwent transplant), compared to	N/R	Age range at follow-up of ADA-SCID group 1-18 years (mean 6.6 years).

Study reference	Country	Study design	Participants	N	Time-frame	Follow-up
				control group of 11 patients who underwent BMT for other SCID conditions.		
Slatter 2008	UK	Retrospective cohort study.	All patients who underwent HSCT for severe T-lymphocyte immunodeficiencies at one centre, who survived more than 2 years. One group treated with anti-CD52 HSCT, the other group treated with anti-CD34.	N=19 long-term survivors from each group.	1987 to 2004.	Follow-up post 2 years survival. Anti-CD52-treated group median 12.83 years (range 1.17-18.92), anti-CD34-treated group median 5.92 years (range 2.67-8.17).
Titman 2008	UK	Observational cohort study.	Children with SCID who had been treated with HSCT at one centre. Participants were eligible if 1 year post-transplant, and 3.5 years or older at time of assessment.	N=105 out of 117 eligible.	1979 to 2003.	Average time since transplantation 7 years and 7 months (range 13 months to 25 years).
Teigland 2013	USA	A prospective/ retrospective study.	SCID patients who received non-ablative T-cell-depleted haploidentical parental BM transplants at this institution who received subsequent transplants from either the same (N=29) or a different (N=20) donor.	N=49 boosted patients, n=122 nonboosted patients.	1982 to 2012.	Up to 28 years post-transplantation.
Wahlstrom 2016 - in press	USA	Retrospective cohort study.	Eligible patients included patients with a diagnosis of SCID who underwent first hematopoietic stem cell transplantation at the University of California San Francisco Benioff Children's Hospital.	N=74.	1988 to 2014.	Median follow up of 7 years (range: 2 months–25 years).
Baffelli	Italy	Retrospective	Children diagnosed at one centre	N=27.	1997 to 2013.	Of the 27 ADA-SCID patients, 7 were

Study reference	Country	Study design	Participants	N	Time-frame	Follow-up
2015		cohort study.	with ADA deficiency.			immediately lost to follow-up because they moved to centers closer to their home. Longest follow up time 15 years.
Cuvelier 2016	Canada	Retrospective cohort study.	All patients were of Mennonite descent.	N=8.	1992 to 2014.	Median of 13.5 years of follow-up (range 1.9–24 years).

Table 13 – Population characteristics of SCID treatment studies - HSCT

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to HSCT	Additional treatment previous to HSCT
Dell Railey 2009	Molecular type of SCID X-linked (gc deficiency) n=53, ADA deficiency n=16, IL-7Ra deficiency n=15, Autosomal recessive SCID defect unknown n=8, RAG1 or RAG2 deficiency n=6, JAK3 deficiency n=6, CD3 chain deficiency n=4, CD45 deficiency n=1, Cartilage hair hypoplasia with SCID n=1, Unknown molecular cause n=1	N/R	N/R	Bone marrow transplant.	N=145 haploidentical parental marrow, and n=16 HLA-identical related marrow.	Of n=37 deceased patients, n=28 (75%) died from viral infections present at the time of diagnosis that continued chronically.	N/R
Sarzotti-Kelsoe 2009	N=60 X-SCID resulting from mutations in the gene encoding the common gamma-chain (γcDef), n=11 Jak3 deficiency, n=15 IL7R deficiency, n=18 ADA	N/R	N/R	Bone marrow transplant.	Unfractionated HLA-identical related (N=8), T cell–depleted HLA-identical related (N=8), or rigorously T cell–depleted	N/R	N/R

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to HSCT	Additional treatment previous to HSCT
	deficiency and n=24 had mutations in other genes, including n=6 RAG-1 or RAG-2 deficiency, n=4 CD3, n=1 CD45, n=1 Artemis, n=11 autosomal recessive SCID of unknown molecular type and n=1 unknown type.				HLA-haploidentical parental (N=112).		
Patel 2008	N=9 patients had X-linked SCID family history, of which 7/9 had molecular defect in the common γ-chain. N=5 had mutations in recombination activating gene 1, of which 4/5 had Omenn syndrome.	Molecular analysis for SCID gene defects was performed on extracted DNA. Adenosine deaminase levels on all patients were assessed.	Individual-level data available.	HLA-identical or haploidentical bone marrow transplantation.	20 MMRD and 5 MRD.	N=12 patients in MMRD group life threatening infections at diagnosis: n=9 pneumocystis jiroveci pneumonia (PCP), n=2 invasive bacterial infections, n=2 cytomegalovirus viremia and n=1 invasive fungal infection. N=1 patient in MRD group life threatening infection at time of diagnosis: concurrent staphylococcal and streptococcal sepsis.	N/R
Patel 2009	Molecular defects known for 16/23 patients. 12/18 patients in MMRD/MUD	N/R	N/R	Hematopoietic stem cell transplantation	5 MRD, 10 haploidentical MMRD, 6 MUD and	Individual patient level data reported	N/R

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to HSCT	Additional treatment previous to HSCT
	group had B+ SCID compared with 4/5 in MRD group.				1 MMUD		
Gennery 2010	49% had B1 SCID (including T2 B1 NK2 phenotype - common g chain or janus kinase 3 (JAK3) deficiency, and T2 B1 NK1 phenotype – IL-7 receptor a deficiency). 29% had B2 SCID (predominantly T2 B2 NK1 phenotype - recombinase activating gene [RAG] 1 or 2, or artemis deficiency). 22% had other forms of SCID, including CD3 subunit deficiency, CD45 deficiency, and other rare molecular defects as well as genetically undefined defects.	International Union of Immunological Societies definitions of SCID or PID.	N/R	Hematopoietic stem cell transplantation. Exact treatment protocols including donor and recipient matching, conditioning regimens and precautions used to prevent risk of infection dependent on time period, individual differences and each centre's individual practice.	<1995: n=84 genotypically HLA identical, n=33 phenotypically HLA identical, n=229 HLA-mismatched and n=15 URD. 1995-1999: n=26 genotypically HLA identical, n=21 phenotypically HLA identical, n=90 HLA-mismatched and n=20 URD. 2000-2005: n=25 genotypically HLA identical, n=14 phenotypically HLA identical, n=96 HLA-mismatched and n=46 URD.	n=379 did not and n=247 did have pre-HSCT respiratory impairment. n=563 did not and n=53 did have pre-HSCT septicaemia. n=432 did not and n=191 did have pre-HSCT viral infection.	N/R
Chan 2011	46% X-linked IL-2 receptor γ chain, 13% adenosine deaminase, 7% recombinase activating genes 1 or 2, 3% IL-7 receptor α chain, 3% Omenn syndrome, 3%	Inclusion as a true SCID or Omenn syndrome case required ≥1 of the following: (i) a specified SCID gene defect; (ii)	Mean/median age at SCID symptom onset: 11/8 weeks. Mean/median	HSCT or enzyme replacement.	n=16 HLA matched sibling HSCT; n=50 haploidentical T-depleted parent HSCT; n=9 adult matched unrelated HSCT, dotted; n=9	N/A	N/A

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to HSCT	Additional treatment previous to HSCT
	Zap-70, 2% Janus kinase 3, 1% CD45, 1% purine nucleoside phosporylase, 21% other or not known.	immunologic diagnosis and treatment at an immunodeficiency centre; (iii) autopsy results provided to the family that confirmed SCID; and (iv) absence of a documented non-SCID immune disorder.	age at SCID diagnosis: 26/24 weeks		matched unrelated cord blood; n=5 PEG-ADA.		
Brown 2011	Sibling cohort: n=14 γ-c, n=3 JAK3, n=3 IL-7RA, n=10 RAG1/2, n=4 artemis, n=1 Omenn, n=8 ADA, n=17 undefined. Proband cohort: n=10 γ-c, n=3 JAK3, n=1 IL-7RA, n=6 RAG1/2, n=2 artemis, n=2 Omenn, n=8 ADA, n=16 undefined.	N/R	Median age of diagnosis of sibling cohort: n=4 antenatal, of the rest median age 0 days (range 0-29 days). Median age of diagnosis in proband group was 143.5 days (range 1-455 days.)	Allogenic hematopoetic stem cell transplantation (1 from sibling cohort received gene therapy due to lack of well-matched donor).	Sibling cohort: n=11 matched sibling donor, n=8 matched family donor, n=5 matched unrelated donor, n=3 mismatched unrelated donor, n=6 cord blood, n=24 haploidentical, n=1 gene therapy autologous. Proband cohort: n=6 matched sibling donor, n=6 matched family donor, n=2	Sibling group treated with prophylactic medication to prevent infections, whereas proband group were not. Where data was available 26/29 probands had at least 1 infection, 25/29 had multiple infections. In the sibling cohort 10/57 patients had a total of 12 infections	N/R

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to HSCT	Additional treatment previous to HSCT
					matched unrelated donor, n=1 mismatched unrelated donor, n=0 cord blood, n=16 haploidentical, n=0 gene therapy autologous.		
Bertrand 1999	N=122 B+ SCID and n=56 B- SCID.	B+ SCID defined as blood T-cells counts <250/ µL and B cell counts >50/µL. B- SCID defined as T-cell counts <250/µL and B cell counts <50/µL. All patients had normal adenosine deaminase enzymatic activity.	N/R	HLA non-identical T-cell-depleted Bone Marrow Transplantation (BMT).	All donors and recipients were related. The compatibility of HLA antigens between donor and recipient was determined by HLA A, B, DR, DQ typing.	N/R	N/R
Giri 1994	n=4 T^-B^-SCID, n=4 T^-B^+SCID, n=1 T+B+SCID, n=1 MHC class I deficiency (bare lymphocyte syndrome), n=1 Wiscott Aldrich syndrome (WAS).	Classification of PID according to WHO Committee for immunodeficiencies.	Median age at diagnosis 8 months (range birth-41 months). N=2 diagnosed at birth due to family history. Remaining patients diagnosed due	Bone Marrow Transplantation.	HLA non-identical Famliy donors.	2/11 had no illness previous to transplant. 9/11 protracted diarrhoea, 9/11 failure to thrive, 8/11 lung infections (5/11 pneumocystis pneumonitis, 1/11 adenovirus pneumonitis, 1/11	From diagnosis to immunological reconstitution, patients received intestinal decontamination by nonabsorbable antibiotics, oral antifungals, oral immunoglobin, monthly

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to HSCT	Additional treatment previous to HSCT
			to clinical presentation of symptoms.			respiratory syncytial viral pneumonia, 1/11 bronchiolitis), 1/11 cytomegalovirus infection. Despite treatment, 5/9 patients had presence of some infection 1 week before BMT.	intravenous globulin and trimethoprim/sulfamethoxazole prophylaxis for pneumocystis pneumonitis.
Honig 2007	ADA-SCID.	Diagnosis of ADA deficiency based on enzyme activity in erythrocytes; n=14 undetectable, n=1 markedly reduced.	Diagnosis of n=2 made due to family history.	Hematopoietic stem cell transplantation; n=12 bone marrow, n=3 peripheral-blood stem cells.	n=7 HLA-matched family donors, n=6 HLA-mismatched family donors, n=2 matched unrelated donors.	N=14 presented up to age 4 months with infections or failure to thrive.	N=2 had received prior enzyme replacement therapy with PEG-ADA, which was discontinued several weeks before transplantation.
Mazzorali 2007	n=30 T^-B+SCID, n=11 JAK3-deficient SCID, n=12 γc-deficient SCID, n=2 IL7R-deficient SCID, n=5 Undefined T^-B+SCID, n=13 T^-B^-SCID, n=4 RAG-deficient SCID, n=4 Artemis-deficient SCID, n=1 ADA deficiency, n=4 undefined T^-B^-SCID.	N/R	N/R	Hematopoietic stem cell transplantation.	n=12 Matched Sibling Donor, n=33 Mismatched Related Donor, n=3 phenotypically identical related donor (PIRD), n=10 Matched Unrelated Donor.	Individual data on organ damage pre-HSCT.	N/R
Myers 2002	Early transplant (first 28 days of life): n=15 γc deficiency (71%), n=2	Early transplant group: diagnosis through known	N/R	Hematopoietic stem cell transplantation.	Early group: 2/21 infants received T-cell-depleted HLA-	N/R	N/R

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to HSCT	Additional treatment previous to HSCT
	ADA deficiency (10%), n=1 Jak3 deficiency (5%) and n=3 (14%) unknown molecular defect inherited in an autosomal recessive pattern. Late transplant (after 28 days of life): n=29 γc deficiency (41%), n=14 ADA deficiency (20%), n=4 Jak3 deficiency (6%) and n=18 (25%) unknown molecular defect. N=3 mutations in recombinase-activating genes, n=2 alpha chain of the IL-7 receptor and n=1 cartilage hair hypoplasia.	family history. 9/21 received diagnosis in utero, 12/21 received diagnosis at birth. Late transplant group: not reported.			identical sibling marrow. 19/21 infants received T-cell-depleted haploidentical parental marrow. Late group: not reported.		
Cipe 2012	N=15 SCID, n=2 Omenn syndrome, n=1 MHC Class II deficiency, n=1 ADA deficiency.	All patients met the diagnostic criteria for primary immunodeficiency disease as defined by ESID-PAGID.	Median age at diagnosis 4 months, range 1.5 to 9 months. N=1 asymptomatic patient diagnosed due to family history. The remaining patients diagnosed after clinical	HLA-HSCT. Time between diagnosis and first transplant = median 1 month (range 0.5 to 2 months).	Haploidentical.	Individual data on infections at diagnosis/ clinical signs and presence of CMV antigenemia.	CMV treatment with ganciclovir was started whenever CMV antigenemia got detected on routine (3x weekly) evaluation.

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to HSCT	Additional treatment previous to HSCT
			presentation.				
Pai 2014	All had classic SCID. N=86 (36%) IL2RG, n=22 (9%) IL7R, n=11 (5%) JAK3, n=14 (6%) ADA, n=1 PNP, n=17 (7%) RAG1/RAG2, n=11 (5%) DCLRE1C, n=2 (1%) CD3D, n=1 CD3Z, n=1 CD45, n=74 (31%) unknown.	Diagnosis of classic SCID based on absolute T-cell count pf <300 per cubic millimetre and an absence of T-cell responses to mitogens.	Median age at diagnosis 138.5 days.	Hematopoietic cell transplantation. Transplants were bone marrow (139/240); mobilised peripheral blood (58/240); or umbilical cord blood (43/240).	n=32 matched sibling donors; n=138 mismatched related donors; n=8 other related donors, n=62 unrelated donors.	171/240 had an infection before transplantation, out of which 106/240 had an active infection at the time of transplantation. 69/240 had never had an infection.	N/R
Neven 2009	Molecular diagnosis: 22/90 IL2RG (γc), 20/90 RAG-1/2, 16/90 JAK3, 12/90 DCLRE1C (Artemis), 6/90 IL7RA, 6/90 unknown, 4/90 reticular dysgenesis, 3/90 ADA SCID, 1/90 CD3E.	N/R	Median age at diagnosis: ≤3 months 35/90 (39%); >3 months 55/90 (61%).	Allogeneic Hematopoietic stem cell transplantation.	22/90 matched sibling, 15/90 pheno-related, 2/90 unrelated, 51/90 mismatched-related.	Symptoms at diagnosis: 16/90 none, 60/90 infections, 40/90 failure to thrive, 8/90 Omenn syndrome, 12/90 maternofetal engraftment.	N/R
Rogers 2001	n=11 ADA-SCID, n=11 non-ADA SCID (n=4 recombinase activating gene defects, n=3 X-linked SCID, n=4 undefined SCID forms).	N/R	N/R	Bone marrow transplantation.	Individual data available.	N=1 had an acute encephalitic illness (presumed to be viral), but this resolved with treatment before transplantation.	N/R
Slatter 2008	Individual data available.	Lymphocytes described as present or absent after flow cytrometry.	N/R	T lymphocyte-depleted hematopoietic stem cell transplantation.	Individual data available.	Individual data available.	N/R

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to HSCT	Additional treatment previous to HSCT
		Immunoglobulin levels described as normal or low using age-specific reference ranges.		Pre-1999 – marrow from HLA-mismatched donors depleted in vitro with anti-CD52 antibody. Post 1999, marrow from CD34 stem cell used. Some patients received cytoreductive chemotherapy.			
Titman 2008	SCID n=43; ADA-SCID n=13; combined immunodeficiency undefined n=19; Wiskott-Aldrich syndrome n=10; Chediak-Higashi syndrome n=3; CGD n=2; CD40 ligand n=4; intractable colitis and immunodeficiency n=2; y-interferon deficiency n=1; XLP/HLH n=2; LAD type 1 n=2; undefined neutrophil defect n=3; XLT n=1.	N/R	Average age at assessment 11 years (range 3.5-25 years).	Hematopoietic stem cell transplant.	35/105 Matched sibling donor (MSD), 9/105 Matched family donor (MFD), 1/105 Mismatched family donor (MMFD), 31/105 Matched unrelated donor (MUD), 10/105 Mismatched unrelated donor (MMUD), 20/105 Haploidentical donor (HAPLO).	N/A	N/A
Teigland 2013	ADA deficient n=6 no booster and n=20 non-boosted, Auto Rec n=6 boosted and n=9 non-boosted, Cartilage hair	Patients met the criteria of the World Health Organization for the diagnosis of	The age at diagnosis ranged from 0 days to 1.7 years	N=1 received a thymus transplant between her second and third	N=2 received HLA-identical donor subsequent transplants. N=42 patients received	N/A	N/A

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to HSCT	Additional treatment previous to HSCT
	hypoplasia n=1 boosted and n=0 non-boosted, CD45Def n=0 boosted and n=1 non-boosted, CD3eDef n=1 boosted and n=0 non-boosted, Cd3zDef n=1 boosted and n=0 non-boosted, Cd3dDef n=0 boosted and n=2 non-boosted, Artemis Def n=0 boosted and n=3 non-boosted, RAG2Def n=5 boosted and n=0 non-boosted, RAG1Def n=1 boosted and n=1, IL7RaDef n=7 boosted and n=17 non-boosted, Jak3Def n=4 boosted and n=5 non-boosted, X-linked n=15 boosted and n=62 non-boosted, unknown n=2 booster and n=2 non-booster.	SCID, and none had 'leaky' SCID or Omenn syndrome.		stem-cell transplants. N=3 received gene therapy elsewhere following three, four and two transplants at this institution, respectively; this was unsuccessful in all cases. 1/3 surviving boosted ADA-deficient patients is receiving PEG-ADA therapy, and all n=3 of the deceased ones received it. N=4 received additional matched unrelated donor transplants at other institutions following transplants at this institution and n=2 subsequently	only haploidentical booster transplants; n=27 from same parent, n=14 from other parent, n=1 from grandmother. N=5 matched unrelated cord blood transplant.		

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to HSCT	Additional treatment previous to HSCT
				died.			
Wahlstrom 2016 - in press	Artemis deficiency (n=19), IL2R-cγ deficiency (n=17), RAG1/2 deficiency (n=13), IL7Ra deficiency (n=7), ADA deficiency (n=2), CD3d deficiency (n=1), DNA PKcs deficiency (n=1), cartilage hair hypoplasia (n=1), reticular dysgenesis (n=1) and n=12 genetic etiology unknown.	Diagnoses were made based on genetic testing when available, or clinical criteria as previously published. "Leaky" SCID was not considered as exclusionary criteria.	N/R	Hematopoietic stem cell transplantation.	Siblings (n=15), mothers (n=44), fathers (n=7), or unrelated donors (n=8).	n= 8 presented pre-transplant GVHD.	N/R
Baffelli 2015	N=27 ADA deficiency.	Diagnosis of ADA deficiency based on RBC and Plasma ADA activity, Adenine Nucleotide content in RBC, IgG Anti-ADA antibody plasma levels, analysis of ADA gene mutations, immunological evaluation and quantitative analysis of chimerism (TRECs).	N=26 had enzymatic and molecular diagnosis performed between 1 and 36 months of age (average 9 months). N=1 prenatal diagnosis was performed after funicolocentes is at the 5th month of pregnancy.	HSCT or PEG-ADA or gene therapy or a combination of these.	Individual data available.	n=18 recurrent severe infections, n=12 failure to thrive, n=8 hyperpyrexia, n=7 candidiasis, n=6 diarrhea, n=6 hypotonia, n=5 bronchitis, n=5 hepatomegaly, n=4 dermatitis, n=4 hypotrophy, n=4 skin involvement, n=1 tremors.	N/R
Cuvelier	N=8 leaky SCID (Zap-70	DNA from buccal	Median of 13	Allogeneic HSCT.	N=3 T cell-depleted	N=5 severe	N/R

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to HSCT	Additional treatment previous to HSCT
2016	deficiency).	swabs or stored pretransplant blood was used to confirm the genetic diagnosis in patients who had undergone HSCT before publication of the original Mennonite genetic mutation.	months (range 12 days to 27 months).		haploidentical peripheral blood stem cell (PBSC) transplants from their mothers, n=3 received 10/10 human leukocyte antigen (HLA)-matched sibling donor bone marrow transplants with no T cell depletion, n=2 underwent unrelated umbilical cord blood transplants.	community-acquired and opportunistic infections characteristic of SCID, n=1 treatment-refractory immune thrombocytopenia purpura (ITP).	

Table 14 – Treatment characteristics of HSCT studies.

Study reference	Definition of early/late	N each group	Age at transplant	Had repeat HSCT	Received conditioning regimen	Conditioning drugs used
Dell Railey 2009	Early group: transplanted <3.5 months of age. Late group: transplanted >3.5 months of age.	Early group N=48, late group N=113.	N/R	28/161 (25%) required 1 or more booster transplants. Need for booster transplants also was related to age at transplant (Fisher exact test, P = .018). 10% of early group required booster transplants, whereas 34% of late	None received conditioning.	N/A

Study reference	Definition of early/late	N each group	Age at transplant	Had repeat HSCT	Received conditioning regimen	Conditioning drugs used
				group required boosters.		
Sarzotti-Kelsoe 2009	N/A	N/A	Individual data available.	31/115 patients had more than 1 transplantation.	None received conditioning.	N/A
Patel 2008	N/A	N/A	Median age at transplant for MMRD group 6.5 months (range 0.5-145 months). Median age at transplant for MRD group 1.8 months (range 0.5-5.0 months).	5/20 (25%) patients in the MMRD group had second transplant; 3/5 patients received 2 transplants; 2/5 received 3 transplants. 0/5 patients in the MRD group were retransplanted.	None received conditioning.	N/A
Patel 2009	N/A	N/A	Median age at first transplant was overall 10 months (range 0.8 to 108 months). MMRD/MUD group: 10 months (range 1 to 108 months); MRD group: (7 months (range 2 to 23 months)	18 patients received 29 haploidentical transplants. 5 patients received 6 MRD transplants.	18/29 haploidentical MMRD, MUD, or MMUD transplants given pretransplantation conditioning, except for 1 patient who received an MMRD transplant and did not receive preconditioning. 2/5 patients given conditioning due to older age.	Pretransplantation conditioning, including busulfan, cytarabine, antithymocyte globulin plus cyclophosphamide, or fludarabine, was performed in 13 patients. Fludarabine and anti-CD52 antibody (Campath-1H) were used in 7 patients, with 1 patient also receiving cyclophosphamide and 2 patients receiving anti-CD45 mAb. Campath-1H alone was used in 1 patient.
Gennery 2010	Three age at transplantation groups (<6	N=289 transplanted <6 months of	Median age at transplant (months) SCID:	Grafted <1995 more than 1 stem cell transplantation: n=8	42% received conditioning. Divided into 4 groups: N=285	No conditioning: 55.09% <1995, 24.56% 1995-1999, 20.35% 2000-2005.

Study reference	Definition of early/late	N each group	Age at transplant	Had repeat HSCT	Received conditioning regimen	Conditioning drugs used
	months, 6-11 months, >12 months).	age, n=253 transplanted 6-11 months of age, n=145 transplanted >12 months of age.	<1995: genotypical HLA identical 5.8; phenotypical HLA identical 6.2; HLA mismatched 7.2; Unrelated donor 13.1. 1995-1999: genotypical HLA identical 6.6; phenotypical HLA identical 4.5; HLA mismatched 6.9; Unrelated donor 10.1. 2000-2005: genotypical HLA identical 4.9; phenotypical HLA identical 4.2; HLA mismatched 7.5; Unrelated donor 9.5.	Genotypically HlA identical, n=3 Phenotypically HLA identical, n=43 HLA-mismatched and n=4 URD. Grafted 1995-1999 more than 1 stem cell transplantation: n=3 Genotypically HlA identical, n=2 Phenotypically HLA identical, n=17 HLA-mismatched and n=2 URD. Grafted 2000-2005 more than 1 stem cell transplantation: n=0 Genotypically HlA identical, n=2 Phenotypically HLA identical, n=23 HLA-mismatched and n=5 URD.	no conditioning, n=297 busulfan containing conditioning, n=69 other chemotherapy, n=29 ATG,Camapath or OKT3 only, n=19 other conditioning or N/A.	Busulfan containing conditioning: 44.11% <1995, 24.58% 1995-1999, 31.31% 2000-2005. Oother chemotherapy: 50.72% <1995, 15.94% 1995-1999, 33.33% 2000-2005. ATG/Campath/OTK3 68.97% <1995, 10.34% 1995-1999, 20.69% 2000-2005. Other conditioning: 100% <1995, 0% 1995-1999, 0% 2000-2005.
Chan 2011	N/A	N/A	Mean/median age at which treatment was initiated: 34/28 weeks.	N/A	N/A	N/A
Brown 2011	No data on age at transplantation but study compares infants	N/A	N/A	N/A	Proband cohort: n=11 unconditioned, n=7 reduced intensity conditioning, n=12 myeloablative. Sibling cohort: n=20 unconditioned, n=20 reduced intensity	N/R

Study reference	Definition of early/late	N each group	Age at transplant	Had repeat HSCT	Received conditioning regimen	Conditioning drugs used
	diagnosed prenatally or at birth to proband infants.				conditioning, n=18 myeloablative.	
Bertrand 1999	Age at transplant (median) for B+ and B- SCID classified into 3 groups: <6 months, 6-12 months, >12 months	<6 months: n=41 B+SCID and n=21 B^-SCID. 6-12 months: n=51 B+SCID and n=26 B^-SCID. >12 months n=30 B+SCID and n=9 B^-SCID.	Median age at transplantation 7 months for B+ SCID and 6.5 months for B- SCID.	The 122 patients with B+ SCID received a total of 146 BMTs, and the 56 patients with B– SCID received a total of 68 BMTs.	37/122 patients with B+ SCID received BMT without a preceding conditioning regimen. 13/56 with B– SCID received BMT without a preceding conditioning regimen.	Patients with B+SCID: 14/122 with cyclophosphamide (with or without antithymocyte globulin), 6/122 with busulfan only (8 or 16 mg/kg), 43/122 with busulfan (8 mg/kg) plus cyclophosphamide (200 mg/kg), 19/122 with busulfan (16 mg/kg) plus cyclophosphamide (200 mg/kg), and 3/122 with other or miscellaneous drugs. Patients with B^-SCID: Cyclophosphamide was given to 4/56 patients, busulfan (16 mg/kg) to 1/56, busulfan (8 mg/kg) plus cyclophosphamide (200 mg/kg) to 21/56, busulfan (16 mg/kg) plus cyclophosphamide (200 mg/kg) to 9/56, and other or miscellaneous drugs to 8/56.
Giri 1994	N/A	N/A	Median age at BMT was 13 months (range 3 weeks to 77 months).	One patient received a second transplant following failure of engraftment.	All patients received pre-transplant conditioning.	n=1 cyclophosphamide 50mg/kgx4d; n=2 cyclophosphamide 50mg/kgx4d and anti-lymphocyte globulin 30mg/kgx3d; n=3 cyclophosphamide

Study reference	Definition of early/late	N each group	Age at transplant	Had repeat HSCT	Received conditioning regimen	Conditioning drugs used
						50mg/kgx4d, anti-lymphocyte globulin 30mg/kgx3d and cytosine arabinoside 80 or 90mg/m^2 twice daily x4d; n=1 cyclophosphamide 50mg/kgx4d, anti-lymphocyte globulin 30mg/kgx3d, busulphan 4mg/kgx4d and cytosine arabinoside 80 or 90mg/m^2 twice daily x4d; n=1 Ara 3 grams/m^2 twice daily x3d and total body irradiation 200 cGy twice daily x3d; n=4 cyclophosphamide 50mg/kgx4d, anti-lymphocyte globulin 30mg/kgx3d and melphalan 140mg/m^2 x1d.
Honig 2007	N/A	N/A	Age at HSCT ranged from 2 months to 2.5 years. 12/15 transplants performed in first 6 months of life. 3/15 transplanted at >6 months of life (2/15 transplants at > 1 year old).	n=2 who first received transplantation without conditioning and failed to engraft so they underwent a second transplant which was successful.	n=7 no conditioning (those receiving transplants from matched family donors), n=8 received conditioning.	Individual data available.
Mazzorali 2007	N/A	N/A	N/R	n=4 required 2 transplantations, n=1 required 3 transplantations.	Individual data available	Individual data available
Myers	Early group:	N(early)=21,	The median age at	Early group: 1/21	Early group: none received	N/R

Study reference	Definition of early/late	N each group	Age at transplant	Had repeat HSCT	Received conditioning regimen	Conditioning drugs used
2002	transplanted in first 28 days of life. Late group: transplanted after first 28 days of life.	N(late)= 96	transplantation for the early group was 10 days (range, 7-24 days). The median age at transplantation for the late group was 190 days (range, 45-516 days).	required booster transplant. Late group: not reported.	pre-transplantation chemotherapeutic conditioning or GVHD prophylaxis. Late group: not reported.	
Cipe 2012	N/A	13/18 patients received stem cells after three months of age.	The median time between the diagnosis and the time of the first transplantation was one month (range, 0.5–2 months).	The most common complication was graft failure (61%), so repeated transplantations were performed in 7/18 (twice in 4/18, three times in 1/18, and four times in 2/18). A total of 30 transplantations were performed in 18 patients.	9/18 patients who tested positive for CMV antigenemia and were not treated with a conditioning regimen.	Cyclosporin A has been the agent of choice for GvHD prophylaxis in 18 of 30 transplantations.
Pai 2014	Early: ≤3.5 months. Late: >3.5 months	Age at transplant ≤3.5 months: n=68 (28%). Age at transplant >3.5 months: n=172 (72%)	Median age at transplantation was 180.0 days.	A boost was defined as an additional transplant from the same donor without conditioning. A second transplant was defined as an additional transplant from a different donor (with or without conditioning) or from the same donor with	120/240 received none, 39/240 immunosuppression, 35/240 reduced intensity and 46/240 myeloblative.	Categories were none, immunosuppression (regimens containing one or more of the following: fludarabine, cyclophosphamide, antithymocyte globulin, or alemtuzumab), reduced intensity conditioning (regimens containing melphalan, anti-CD45 antibodies, 200 to 400 cGy of

Study reference	Definition of early/late	N each group	Age at transplant	Had repeat HSCT	Received conditioning regimen	Conditioning drugs used
				conditioning. 23/240 had received a boost at 5-year follow-up. 34/240 had received a second transplant at 5-year follow-up. 11/240 had received both a boost and a second transplant at 5-year follow-up.		total-body irradiation, or busulfan administered at a total dose of <12 mg per kg of body weight), and myeloablative conditioning (regimens containing busulfan at a total dose ≥12 mg per kg).
Neven 2009	N/A	N/A	Age at HSCT: ≤3 months 23/90 (25%); >3.5 months 67/90 (75%).	Number of HSCTs per patient: 90/90 one transplant, 7/90 two transplants, 3/90 three transplants. 12/90 received 1 or 2 boosts 2.5 to 15 years post-HSCT.	46/90 received no conditioning.	5/90 received immunosuppression only, 22/90 received Bu 8/Cy 200 mg/kg, 17/90 received Bu 16/Cy 200 mg/kg. GVHD prophylaxis: 52/90 T delpletion, 32/90 cyclosporin A.
Rogers 2001	N/A	N/A	Age range at transplant for ADA-SCID group 1-51 months (mean 9 months) and 11 months (range, 1 to 60 months) for the control group.	N/R	Individual data available.	Conditioning had a busulphan/ cyclophosphamide-based regimen, except for patient 10, who was conditioned with fludarabine and melphalan cytotoxic therapy. Patients 9 and 10 received PEG-ADA for 36 and 2 months, respectively, before undergoing transplantation.
Slatter 2008	N/A	N/A	Age at transplantation: anti-CD52 group median 7 months, range 1.25-17	Individual data available.	Individual data available.	Individual data available.

Study reference	Definition of early/late	N each group	Age at transplant	Had repeat HSCT	Received conditioning regimen	Conditioning drugs used
			months. Anti-CD34 group median 6 months, range 1-25 months.			
Titman 2008	N/A	N/A	Average age at transplant 3 years 6 months (median 13 months). Younger than 3 years at transplantation N=66, older than 3 years at transplantation N=39.	N/A	44/105 Full, 36/105 Reduced intensity, 23/105 None.	Full intensity conditioning was defined as busulphan (16-20 mg/kg) and cyclophosphamide (200 mg/m2) with or without serotherapy. Most patients with reduced intensity transplantations received fludarabine (150 mg/kg) and melphalan (140 mg/m2) with serotherapy (either Campath 1H or antithymocyte globulin), although other reduced intensity transplantations regimens, including fludarabine/ cyclophosphamide, were used in a minority of patients.
Teigland 2013	N/A	N/A	The average age at initial transplantation for those who are currently alive was 194 days (s.d. 111) and for those who are deceased, the average age at initial transplantation was 273 days (s.d.	N=40 received 1–3 subsequent transplants from either the same (N=29) or a different (N=20) donor for a total of 81 additional transplants. N=3 patients received gene therapy elsewhere following three, four and two transplants at	Conditioning was used only in patients who received matched unrelated donor cord blood transplants (N=5).	N/R

Study reference	Definition of early/late	N each group	Age at transplant	Had repeat HSCT	Received conditioning regimen	Conditioning drugs used
			148).	this institution, respectively; this was unsuccessful in all cases.		
Wahlstrom 2016 - in press	Age at transplantation divided into 4 groups: 0-3.5 months, 3.5-6 months, 6-12 months, >12 months. N provided for each group.	N(0-3.5 months)=32, N(3.5-6 months)=13, N(6-12 months)=18, N(>12 months)=11	Median of 139 days of life (ranging from 13 days to 25.6 months old).	n=15 required a second transplant.	Bone marrow from matched or single allele-mismatched donors was given unmanipulated except for RBC or plasma depletion, depending on ABO mismatch.	Patients undergoing matched or single mismatched HSCT typically received GVHD prophylaxis with cyclosporine +/- methotrexate or mycophenolate mofetil. Chemotherapy only n=3 TME+, n=3 TME-; serotherapy only n=6 TME+, n=8 TME-; both n=4 TME+, n=13 TME-; unconditioned n=22 TME+, n=15 TME-.
Baffelli 2015	N/A	N/A	Individual data available.	Individual data available.	Individual data available.	Individual data available.
Cuvelier 2016	N/A	N/A	Individual data available.	n=1 (patient #6) required one boost, n=1 (patient #2) required second transplant.	n=5 yes, n=3 no (all matched sibling bone marrow donors).	n=5 received myeloablative conditioning regimens with busulfan and either cyclophosphamide or fludarabine +/− rabbit anti-thymocyte globulin (including the three haploidentical PBSC and both cord blood transplants).

Table 15 – Survival outcomes and statistical analyses associated with age at transplant - HSCT

Study reference	Survival before transplant	Survival after transplant	Statistical analyses on age at transplant
Dell Railey	N/A	Survival in early group: 45/48 (8-year	This difference in survival is statistically significant with a

Study reference	Survival before transplant	Survival after transplant	Statistical analyses on age at transplant
2009		Kaplan-Meier survival, 96%; 95% CI, 84% to 99%). Survival in late group: 70% (95% CI, 60%-77%).	log rank P value of .0017. Patients transplanted after 3.5 months of life had a lower survival rate (P=.0049), with a hazard ratio of 1.032 per 10-day increase in age at transplant (95% CI, 1.010-1.056)
Sarzotti-Kelsoe 2009	N/A	N/R	None
Patel 2008	N/A	MMRD: 10/20 survived at median age 15.2 years. MRD: 5/5 survived at median age 23.3 years. Individual data available.	None
Patel 2009	N/A	Donor cell engraftment and survival occurred in 13 (72%; 95% CI, 46% to 89%) of 18 MMRD/MUD transplant recipients and 5 (100%; 95% CI, 46% to 100%) of 5 MRD transplant recipients (P=0.4, Kaplan-Meier curve)	None
Gennery 2010	N/A	SCID 3 year survival percentage (95% CI): <1995 - genotypical HLA identical: 81 (73-90); phenotypical HLA identical 57 (41-78); HLA mismatched 49 (43-56); Unrelated donor 53 (33-86). 1995-1999: genotypical HLA identical: 84 (69-100); phenotypical HLA identical 80 (62-100); HLA mismatched 69 (60-79); Unrelated donor 68 (48-97). 2000-2005: genotypical HLA identical: 90 (77-100); phenotypical HLA identical 83 (58-100); HLA mismatched 66 (55-78); Unrelated donor 69 (54-89).	Univariate analysis: Transplanted <6 months: N=289, absolute N(deaths)=79, 10-year survival % (95% CI) = 68 (62-74). Transplanted 6-11 months: N=253, absolute N(deaths)=92, 10-year survival % (95% CI) = 59 (53-67). Transplanted >12 months: N=145, absolute N(deaths)=61, 10-year survival % (95% CI) 51 (42-61). p=.0008. Multivariate analysis: Transplanted <6 months: Hazard ratio (95% CI)=1. Transplanted 6-11 months: Hazard ratio (95% CI) = 1.3 (0.9-1.9), P=.11. Transplanted >12 months: Hazard ratio (95% CI): 2.4 (1.6-3.5), p<.0001
Chan 2011	51% of deaths occurred in diagnosed infants after receiving HSCT or enzyme replacement. Twelve infants	Mean/median age at death, if deceased: 117/45 weeks. 61/158 SCID infants had died at the time of the survey, giving	Those 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

Study reference	Survival before transplant	Survival after transplant	Statistical analyses on age at transplant
	(20%) did not receive definitive treatment, but did have a diagnosis prior to their death, and 17 of the 61 deceased infants (29%) had their diagnosis made only after their death.	overall survival rate of 61% (95%CI 54-69%). 51% of deaths were in diagnosed infants after HSCT or enzyme replacement therapy. 12/61 (20%) of infants who died did not receive treatment although were diagnosed prior to death. 17/61 (29%) infants who died diagnosed only after death. Overall survival rate of treated infants = 81.4%. Post year 2000 survival rate of treated infants = 87.2%.	weeks (Fig. 5). There was a statistically significant difference between the mean age of 29 weeks in those who survived and 57 weeks in those who died (p=0.038).
Brown 2011	Of the 48 probands, n=17 (35.4%) died before allogeneic HSCT; and in all cases where data were available, the cause of death was an infectious complication. Of the sibling cohort, n=1 of the 60 patients died before HSCT, again of infection, and this was in a family who refused transplantation for the child	Sibling group 5/59 died (8.5%), Probands 12/31 died (39%). Overall mortality: Siblings 6/60 (10%), Probands 29/48 (60%). In a subcohort analysis of probands/siblings that were transplanted within 10 years of each other, 54% (13 of 24) probands survived compared with 93% (29 of 31) siblings, suggesting that, even if transplanted within 10 years of each other, there is still a significant improvement in outcome in SCIDs diagnosed at birth.	None
Bertrand 1999	Presence of pre-transplant lung infection increased odds of death in both groups.	Survival analysis by product-limit method and comparisons of survival distribution by log-rank test. At follow-up, 73/122 B+ SCID patients and 20/56 patients with B-SCID were alive with T cell engraftment after BMT. 2 additional B+ SCID were alive after second BMT. Factors influencing survival included age at BMT, but only for patients with B+ SCID; and time period of BMT (survival higher after 1991).	Age at BMT also had a significant impact on survival with engraftment for patients with B+ SCID (73% <6 months of age vs 53% >6 months of age) (stratified log-rank, P < .05), but not for patients with B– SCID (42% vs 31%) (stratified log rank, NS). Whatever the age at BMT, the results were significantly better for patients with B+ SCID than for those with B-SCID (P = .001).

Study reference	Survival before transplant	Survival after transplant	Statistical analyses on age at transplant
Giri 1994	2/8 patients with lung infection before transplant survived. 0/5 with infection the week before transplant survived.	5/11 patients (46%) alive with immune reconstitution at follow-up of 6-78 months. 6/11 patients died.	Correlation of pre-BMT clinical status with transplant outcome: 2/8 survivors with lung infection before BMT (p=0.06). 3/9 survivors with protracted diarrhoea before BMT (p=0.11). 3/9 survivors with malnutrition before BMT (p=0.11) 5/6 survivors scoring >70 in Karnofsky's scale before BMT and 0/5 survivors scoring < 70 in Karnofsky's scale before BMT (p=0.01). None of 5 with infection in the week before transplant survived (p=0.01). 4/6 survivors <1 year age at BMT and 1/5 survivors >1 year age at BMT (p=0.18)
Honig 2007	N/R	HLA-identical family donor: 7/7 alive at mean follow-up 9.5 years. MMFDs: 4/6 alive, MUD 1/2 alive at mean follow-up 14.6 years.	None
Mazzorali 2007	N/A	42/58 (72.4%) patients alive at follow-up: 90% (9/10) for recipients of MSD-HSCT; 60.6% (20/33) for MMRD-HSCT; 83.3% (10/12) for MUDHSCT, and 3/3 for PIRD-HSCT.	None
Myers 2002	N/A	Early group 20/21 (95%) and late group 71/96 (74%) are alive.	Before transplantation, the late group had a higher mean number of CD3 cells (P=.05). Infants receiving transplants within the first 28 days of life (n=20) had increased T-cell proliferation to PHA at 91 through 120 days, 121 through 180 days, and 181 through 270 days after transplantation compared with those receiving transplants late (n=69) (P=.05). The early group had increased numbers of CD3 cells at 271 days to 1 year, 1 to 2 years, and 2 to 3 years after transplantation (P=.05). The early group had increased numbers of CD45RA T cells at 91 through 120 days, 1 to 2 years, and 2 to 3 years after transplantation (P=.05). These numbers gradually declined and were comparable to the late group by 6 years after transplantation. Patients receiving transplants early had higher TREC values at 91 through 180 days and 181 days

Study reference	Survival before transplant	Survival after transplant	Statistical analyses on age at transplant
			to 1 year after transplantation (P=.01). The mean TREC value peaked at 181 days to 1 year in those receiving transplants early and at 1 to 3 years in those receiving transplants late.
Cipe 2012	N/R	10/15 patients with SCID survived with stable complete donor chimerism. All 3 non-SCID patients died.	None
Pai 2014	N/A	Overall survival rate at 5 years was 74% (178/240 children). 45/240 children received second transplant. Of these, 5 year survival was 56% (26/45). Age at transplant associated with survival. Infants receiving transplant at 3.5 months or younger had 94% 5 year survival rate (64/68). Children >3.5 months at transplant with no history of infection had 90% 5 year survival rate (21/23), and those >3.5 months whose infection had resolved at time of transplant had 82% 5 year survival (48/58). Those > 3.5 months with active infection at transplant had 50% 5 year survival rate (45/91). Infants in early group had higher survival rates regardless of donor type or conditioning.	**Family history:** yes N(0-3.5 months)=58, N(>3.5 months)=31; no N(0-3.5 months)=9, N(>3.5 months)=124; p<0.001. **Infection at treatment:** diagnosed and not cleared N(0-3.5 months)=15, N(>3.5 months)=91; diagnosed and cleared N(0-3.5 months)=7, N(>3.5 months)=58; p<0.001. **Respiratory infection:** yes N(0-3.5 months)=3, N(>3.5 months)=47; no N(0-3.5 months)=65, N(>3.5 months)=125; p<0.001. **DNA viral infection:** yes N(0-3.5 months)=4, N(>3.5 months)=22; no N(0-3.5 months)=64, N(>3.5 months)=150; p=0.121. **CMV infection:** yes N(0-3.5 months)=3, N(>3.5 months)=14; no N(0-3.5 months)=65, N(>3.5 months)=158; p=0.409. **Failure to thrive:** yes N(0-3.5 months)=16, N(>3.5 months)=96; no N(0-3.5 months)=52, N(>3.5 months)=76; p<0.001. **Multivariate analysis - survival, age at transplant and infectious status** p<0.001; >3.5 months active infection p<0.001; >3.5 months infection resolved p=0.075; >3.5 months no infection p=0.969; >3.5 months active infection vs no infection p=0.001; >3.5 months, active infection versus infection resolved p<0.001; >3.5 months infection resolved vs no infection p=0.190. (Other data reported in multivariate analysis: total N, # events, 5 yr OS% and Hazard ratio)
Neven 2009	N/R	Boost transplantation: 12/90 (12%) received 1 or 2 boosts 2.5 to 15 years after first HSCT; mortality: 8/90 (9%) patients died 2.5 to 11 years after	Univariate analysis of age at transplantation but data not reported because negative factors in the analysis were not represented.

Study reference	Survival before transplant	Survival after transplant	Statistical analyses on age at transplant
		transplantation.	
Rogers 2001	N/A	N/A (Only patients who survived transplant and were under follow-up were included in the study).	Correlation of IQ with age at transplantation did not reveal any significant relationship.
Slatter 2008	N/A	N/R - Only those who had survived more than 2 years post-HSCT were included in the study.	None
Titman 2008	N/A	N/A	Early group mean IQ score=85.2 (SD=24.2), late group mean IQ score 85.8 (SD=17.5), p=.90 (ie. No association between early transplantation and lower or higher IQ score). Mean IQ score for ADA-deficient SCID was significantly lower than SCID and CID (p<.01).
Teigland 2013	N/A	75% survival for entire group. Boosted survival rate 63% (dead 18/49). Non-boosted survival rate 80.3% (dead 24/122).	The average age at initial transplantation for those who are currently alive was 194 days (s.d. 111) and for those who are deceased, the average age at initial transplantation was 273 days (s.d. 148). This difference was found to be significant (t= 2.1117, N=49, P=0.0401). Patients who required booster transplantation were an average of 223 days old at initial transplantation (s.d. 131), whereas patients who did not require booster transplantation were an average of 165 days at initial transplantation (s.d. 152). This difference was significant (t=2.3358, N=171, P=0.0207).
Wahlstrom 2016 - in press	N/A	72 patients survived >100 days post-transplant. Overall survival of the entire cohort was 80% with a median follow up of 7 years. Long-term event-free survival, defined as survival without the need for second (conditioned) transplant, was 67.6%.	Univariate analysis was performed examining the association between development of acute GVHD and age at transplant. No significant association was found.
Baffelli 2015	N/A	N/R	None
Cuvelier 2016	N/A	N=8 (100%).	None

Table X. Long-term outcomes and complications after HSCT.

Study	No problems/considered healthy?	Weight <3rd percentile/ enteral feeding	Reported Health Perception	Regular antibiotics required?
Dell Railey 2009	No clinical problems in the previous 2 years were reported in 49% of the patients transplanted early versus 29% in those transplanted late (χ^2, P = .037); this is significantly different.	5% of patients transplanted early less than 3rd percentile for height compared with 17% of those transplanted late (difference not significant), and 2% of those transplanted early compared with 17% of those transplanted late (Fisher exact test, P = .029) were less that the 3rd percentile for weight.	Ninety-five (86%) of the 111 patients were considered by their family to be healthy.	No significant difference between early and late. Standing antibiotics were given to 30/111 (27%).
Sarzotti-Kelsoe 2009	N/R	N/R	N/R	N/R
Patel 2008	Individual data available	N/R	N/R	N/R
Patel 2009	N/R	N/R	N/R	N/R
Gennery 2010	N/R	N/R	N/R	N/R
Chan 2011	N/R	N/R	N/R	N/R
Brown 2011	N/R	N/R	N/R	N/R
Bertrand 1999	N/R	N/R	N/R	N/R
Giri 1994	5/11 alive with immune reconstitution are well and at home without any signs of infection for 6 to 78 months post-BMT.	N/R	N/R	N/R
Honig 2007	n=12 long-term survivors are in excellent health and have no clinical complications.	N/R	N/R	N/R
Mazzorali 2007	24/40 do not require any treatment	Individual data available for weight and length.	N/R	N/R

Study	No problems/considered healthy?	Weight <3rd percentile/ enteral feeding	Reported Health Perception	Regular antibiotics required?
Myers 2002	N/R	N/R	N/R	N/R
Cipe 2012	N/R	N/R	N/R	N/R
Pai 2014	N/R	N/R	N/R	N/R
Neven 2009	58/82 do not require any form of treatment	6/82 require enteral feeding for anorexia	N/R	17/82 need infection prophylaxis via immunoglobulin substitution, antibiotic treatment or both.
Rogers 2001	N/R	N/R	N/R	N/R
Slatter 2008	Individual data available	Individual data available	N/R	N/R
Titman 2008	N/R	N/R	N/R	N/R
Teigland 2013	N/R	N/R	N/R	N/R
Wahlstrom 2016 - in press	N/R	N/R	N/R	N/R
Baffelli 2015	N/R	N/R	N/R	N/R
Cuvelier 2016	3/3 unconditioned patients no appreciable long-term complications by 14, 17, and 21.5 years post-HSCT. Individual data available on significant infections in the first 6 months post-HSCT.	n=1 (Patient 7) experienced severe malnutrition necessitating gastrostomy tube feeding because of chronic GVHD of the gastrointestinal tract	N/R	N/R

Table 17. Long-term outcomes and complications, continued.

Study	Intravenous immunoglobulin	Liver	ADHD	Developmental delay	GvHD	Other
Dell Railey	Replacement	2	21% of entire cohort	No significant difference	No patient died of	Episodes of sinusitis,

Study	Intravenous immunoglobulin	Liver	ADHD	Developmental delay	GvHD	Other
2009	immunoglobulin intravenous (IGIV) administered to 64/111 (58%)	transplant	had ADHD. No statistical difference between early/late.	between early and late groups. 11/111 (10%) had developmental delay.	graft-versus-host disease. Skin GVHD was present in 4 patients, in 2/4 was chronic.	pneunomia and asthma were similar among both groups. More patients transplanted late had problems with diarrhea, oral aversion and persistent rashes including HPV, although no statistically significant differences.
Sarzotti-Kelsoe 2009	N/A	N/A	N/A	N/A	N/A	Data on lymphocyte phenotypes, T cell function and thymic function.
Patel 2008	N/A	N/A	N/A	8/10 MMRD survivors attending or attended school or college, 2 being home-educated. 4/5 MRD survivors attended school, 1/5 home-educated. 3/5 in MRD group performed at the college level. Individual data available.	Acute GvHD (grade I-IV) was present in all patients. Individual data available.	N/A
Patel 2009	5 (38%) of 13 survivors in the MMRD/MUD group. Three of these 5 patients have received HSCT less than 24 months ago	N/R	N/R	School attendance: 82% MMRD group with conditioning; 100% MMRD/MUD with conditioning; 100% MRD group.	Acute GvHD of grade II to IV in 2 (11%) of 18 MMRD/MUD (1 nonconditioned) patients, and 1 patient died despite treatment of the GvHD. Acute GvHD did not occur in the MRD group. 0/23 has chronic GvHD.	MMRD/MUD group with conditioning: respiratory diseases (asthma, n 5 3), dermatologic conditions (eczema, n 5 2; warts, n 5 1), infectious complications (chronic human herpes virus 6 infection, n 5 1), hematologic

Study	Intravenous immunoglobulin	Liver	ADHD	Developmental delay	GvHD	Other
						abnormalities (anemia, n 5 4, autoimmune in 2 cases and iron deficient in 2 cases), gastrointestinal disorder (eosinophilic enterocolitis, n 5 1), speech delay (n52), and dental caries (n51). MRD group respiratory abnormalities (asthma, n52), dermatologic manifestations (viral source warts, n 5 1), infectious complication (chronic human herpes virus 6 infection, n51), obesity (n52), and dental caries (n 5 1).
Gennery 2010	N/A	N/A	N/A	N/A	N/A	N/A
Chan 2011	N/A	N/A	N/A	N/A	N/A	N/A
Brown 2011	N/A	N/A	N/A	N/A	N/A	N/A
Bertrand 1999	N/A	N/A	N/A	N/A	Acute GvHD > grade II: 12% B+SCID and 18% B^-SCID. Chronic GvHD: 32% B+SCID and 36% B^-SCID.	Info on engraftment and modality of T cell-depletion.
Giri 1994	N/A	N/A	N/A	N/A	Individual data available.	Individual data available for HLA match, engraftment and immunologic reconstitution after BMT. Info on chimerism

Study	Intravenous immunoglobulin	Liver	ADHD	Developmental delay	GvHD	Other
Honig 2007	N/A	N/A	Individual data available	Individual data available	Individual data available.	Individual data available on neurologic and cognitive deficits.
Mazzorali 2007	Individual data available. 5/40 require IVIGs.	N/A	N/A	N/A	Individual data available	Individual data available for pubertal development, thyroid function, dentition, neurology, vision, hearing, school attendance, clinical manifestations, autoantibodies, organ damage post-HSCT, respiratory problems, drugs currently needed, hospitalizations since 1y after HSCT and other problems.
Myers 2002	early group: 13/20 (65%) receive monthly IVIG infusions. 7/20 have normal antibody functions.	N/A	N/A	N/A	Early group: 13/21 were free of GvHD. 8/21 developed GvHD out of which 5/8 had grade 1 GvHD, 2/8 grade 3 GvHD and 1/8 grade 4 GvHD.	N/A
Cipe 2012	2/18 patients receiving prophylactic IVIG replacement therapy despite full immune reconstitution, one is at the	N/A	N/A	N/A	7/18 had post-HSCT acute/chronic GvHD ≤ Grade II; all resolved with standard therapy. Individual data available.	4/18 veno-occlusive disease post-HSCT. 7/18 disseminated BCGitis post-HSCT. 3/18 autoimmune thyroiditis requiring l-thyroxin treatment, diagnosed at different repeated times post-HSCT. Individual

Study	Intravenous immunoglobulin	Liver	ADHD	Developmental delay	GvHD	Other
	fourth month of HSCT, one because of complications arising from malnutrition.					data on: lympoid engraftment (TREC), chimerism, transplantation-related early complication, disseminated BCG.
Pai 2014	74/136 had independence from IVIG therapy.	N/A	N/A	N/A	20/236 had acute GVHD of grade 2-4 at 100 days. 8/236 had acute GVHD of grade 3-4 at 100 days. 15/233 had chronic GVHD at 2yr.	N/A
Neven 2009	17/82 need infection prophylaxis via immunoglobulin substitution, antibiotic treatment or both.	N/A	1/82 developed hyperactivity in childhood	1/82 presented severe mental retardation and epileptsy. Patients older than 10 years, 58/62 had school performances within the normal range.	31/90 grade ≥ 2 (18/31 grade 2, 12/31 grade 3, 1/31 grade 4), 24/90 chronic GVHD <2y	1/82 developed schizophrenia in adulthood
Rogers 2001	N/A	N/A	ADA group: none receiving treatment for hyperactivity or behavioural problems.	N/A	N/A	N/A
Slatter 2008	Individual data available	N/A	Individual data available	Individual data available	Individual data available	N/A
Titman 2008	N/A	N/A	N/A	Of 92 children still in school, 27% had a Statement of Special Educational Needs. 9/92 children attending school for children with special needs and/or learning difficulties.	N/A	Mean Full Scale IQ score for the whole cohort was 85.4. Mean SCID IQ score 90.7, mean CID IQ score 89.1, mean ADA deficient SCID IQ score 64.9, mean

Study	Intravenous immunoglobulin	Liver	ADHD	Developmental delay	GvHD	Other
				n=12 were older than 18 years and had left school. 5/12 studying for higher qualifications or in vocational training, 2/12 were unemployed, and 5/12 were in full-time employment.		Wiskott Aldrich Syndrome IQ score 91.6. Mean Chediak Higashi IQ score 66.3, mean other diagnosis IQ score 83.5.
Teigland 2013	N/A	N/A	N/A	N/A	54/171 SCID patients transplanted at this institution since 1982, developed GVHD	N/A
Wahlstrom 2016 - in press	N/A	N/A	N/A	N/A	Post-transplant acute GVHD of any grade developed in 36.5% of patients. Grade II-IV aGVHD diagnosed in 28.4% of all patients, Grade III-IV aGVHD in 9.5% of all patients. 6/72 evaluable patients who survived >100 days post-transplant, had GVHD; 3 of these developed extensive chronic GVHD.	N/A
Baffelli 2015	N/A	N/A	N=1 shows hyperactivity	N=1 shows mild intellectual disability	N/A	N/A
Cuvelier 2016	7/8 patients discontinued IVIg supplement with normal IgG levels. 1/8 still	N/A	N/A	N/A	6/8 acute GVHD (n=3 grade II and n=3 grade III) affecting the skin (n = 6) and gastrointestinal tract	N/A

Study	Intravenous immunoglobulin	Liver	ADHD	Developmental delay	GvHD	Other
	receiving periodic IVIg infusions.				(n= 2). N=4 chronic GVHD (n=2 limited and n=2 extensive) with n=3 eventual complete resolution. N=1, with grade III acute GVHD, had progressive extensive chronic GVHD of the skin, mouth, and possibly lungs. Still severely affected 1.9 years post-HSCT, remains on intensive systemic and topical immunosuppression.	

Table 18 – Study characteristics of SCID treatment studies - gene therapy.

Study reference	Country	Study design	Participants	N	Time-frame	Follow-up
Cicalese 2016 (long-term follow-up of Aiuti 2009)	Italy	Cohort study	Patients with ADA-SCID for whom an HLA-identical family donor was not available and (1) had received ≥6 months of PEG-ADA treatment with demonstrated inefficacy or intolerance or (2) for whom PEG-ADA was not a long-term treatment option.	N=18	Data cut May 8, 2014	Follow-up period ranging from 2.3 to 13.4 years; median, 6.9 years.
Hacein-Bey-Abina 2014	France, UK, USA	Cohort study	Patients who had immunologic profiles characteristic of SCID-X1 and who either lacked a HLA-	N=9	Not reported.	Median follow-up of 29.1 months (range, 12.1 to 38.7).

Study reference	Country	Study design	Participants	N	Time-frame	Follow-up
			identical related or unrelated donor or had an active, therapy-resistant infection, in parallel phase 1/2 trials			

Table19 – Population characteristics of SCID treatment studies - gene therapy.

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to treatment	Additional treatment previous to gene therapy
Cicalese 2016 (long-term follow-up of Aiuti 2009)	ADA-deficiency	ADA mutation analysis	Not reported.	Gene-transduced autologous CD34+ cells.	All were autologous transplants	n=8 failure to thrive, n=7 abnormal findings on brain magnetic resonance imaging, n=6 psychomotor retardation or delayed development and n=5 auditory abnormalities. N=40 severe infections occurred in 14 patients. n=14 had neurologic, CNS, or hearing impairments.	3/18 HSCT, 13/18 PEG-ADA, 2/18 HSCT and PEG-ADA. For patients on PEG-ADA, Enzyme Replacement Therapy was discontinued at a median of 18 days (range, 10-22) before gene therapy (GT).
Hacein-Bey-Abina 2014	SCID-X1	Confirmed genetic mutations	Not reported.	SIN γ-retrovirus gene therapy	All were autologous transplants	8/9 had infection(s) present at time of GT, 1/9 none.	Not reported.

Table 20 – Treatment regimen of studies using gene therapy.

Study reference	Definition of early/late	N early/late group	Age at treatment	Had repeat treatment	Received conditioning regimen	Conditioning drugs used	Conditioning method
Cicalese 2016 (long-term	Not reported.	Not reported.	Median age of 1.7 years (range, 0.5 to	N=1 received a second GT treatment.	Yes, 18/18 received conditioning.	Low-dose busulfan.	2mg/kg per day divided into 4 doses of 0.5 mg/kg on days 23

Study reference	Definition of early/late	N early/late group	Age at treatment	Had repeat treatment	Received conditioning regimen	Conditioning drugs used	Conditioning method
follow-up of Aiuti 2009)			6.1 years).				and 22. The total final dose of busulfan was 4 mg/kg, ;25% of the typical myeloablative regimen.
Hacein-Bey-Abina 2014	Not reported.	Not reported.	Median age 8.0 months	N=2 had second transfusion 1 month and 17.5 months after initial infusion, respectively. N=1 had HSCT (mismatched umbilical-cord-blood transplant) 8 months after gene therapy.	n=2 received conditioning, n=7 no conditioning.	n=1 received two doses of fludarabine (total, 80 mg per square meter of body-surface area), on days -3 and -2. N=1 received three doses of rabbit antithymocyte globulin (total, 13 mg per kilogram of body weight), on days -23, -13, and -11.	Not reported.

Table 21 – Survival outcome and statistical results in studies using gene therapy as SCID treatment.

Study reference	Survival before transplant	Survival after transplant	Statistical analyses on age at transplant
Cicalese 2016 (long-term follow-up of Aiuti 2009)	N/A	100% over 2.3 to 13.4 years (median, 6.9 years).	N/R
Hacein-Bey-Abina 2014	N/R	n=1 deceased and n=8 survived.	N/R

Table 22 – Study characteristics of SCID treatment studies comparing HSCT to gene therapy.

Study reference	Country	Study design	Participants	N	Time-frame	Follow-up
Touzot 2015 ***note that all GT patients have been included in trials reported in Bazian	France	Retrospective cohort study	SCID-X1 patients who lacked an HLA identical donor having undergone haploidentical hematopoietic stem cell transplantation (HSCT) or gene	n=13 HSCT, n=14 gene therapy (***note that all GT patients have been included in trials	March 1999 to December 2013	GT group median 12 years (range 1-15). HSCT group median 6 years (range 1-12)

Study reference	Country	Study design	Participants	N	Time-frame	Follow-up
review (patients GT1-GT9) or Hacein-Bey-Abina 2014 (patients GT10-GT14).			therapy over the same period at a single center level	reported in Bazian review (patients GT1-GT9) or Hacein-Bey-Abina 2014 (patients GT10-GT14)).		

Table 23- Population characteristics of SCID treatment studied comparing HSCT to gene therapy.

Study	SCID Subtype	Diagnostic method	Age at diagnosis	Treatment	Donor type	Illness previous to treatment	Additional treatment previous to transplant/gene therapy
Touzot 2015	SCID -X1 (γc deficiency)	Not reported	Not reported	Haploidentical HSCT or gene therapy using LTR-driven γ-retrovirus.	HSCT group n=6 mother, n=7 father. GT autologous.	SCID -X1 (γc deficiency).	Not reported.

Table 24 – Treatment regimen of studies comparing HSCT to gene therapy.

Study reference	Definition of early/late	N early/late group	Age at transplant	Had repeat HSCT	Received conditioning regimen	Conditioning drugs used	Conditioning method
Touzot 2015	Not reported.	Not reported.	Median age GT 8 months (range 1-11), HSCT 7 months (range 1-15).	n=3 in HSCT group had second transplant. N=1 in GT group underwent HSCT 8 months after GT failed to engraft.	n=1 in GT group and n=13 in HSCT group.	GT patient: 2 doses of fludarabine (total, 80 mg/m2 of body surface area) on days -3 and -2. HSCT patients: 2 infusions of 2.5 mg/kg rabbit antithymoglobulin (r-ATG, Thymoglobuline; Genzyme) on days -2 and -1.	Not reported.

Table 25 – Survival outcome and statistical results in studies comparing HSCT to gene therapy as SCID treatment.

Study reference	Survival before transplant	Survival after transplant	Statistical analyses on age at transplant
Touzot 2015	N/R	n=2 died in HSCT group (n=1 respiratory viral infection, n=1 poor immune reconstitution). N=2 in GT group died (n=1 adenoviral infection, n=1 leukemia).	Resolution of disseminated BCG infection was fastest in GT group (median, 11 months; range, 8.9-14.6 months) than HSCT group (median, 25.5 months; range, 24.1-28.7 months; P=.029). Number of days of infection-related hospitalization was 0.4 and 0.03 days per patient per year in the HSCT and GT groups, respectively (P=.001).

Table 26 – Long-term outcomes other than survival in studies comparing HSCT to gene therapy.

Study reference	No problems/ considered healthy	Leukemia	PEG-ADA	Weight <3rd percentile/enteral feeding	Infections	Require immune-supressive drugs	Reported Health Perception	Requires regular antibiotics	Intravenous immunoglob-ulin	ADHD	Develop-mental delay	GvHD
Touzot 2015	7/13 HSCT patients developed treatment-related complications. Immune dysfunction in 3/13 HSCT patients.	4/14 GT patients developed T-cell acute lymphoblastic leukaemia (30, 33, 34 and 68 months after GT).	Not reported.	Not reported.	Not reported.	Not reported.	11/11 surviving HSCT patients alive and well at follow-up. 12/12 surviving GT patients alive and well at follow-up.	Not reported.	Of patients evaluable for long-term B-cell reconstitution, 10/10 HSCT patients were receiving IVIG and 4/12 GT patients were no longer receiving IVIG.	Not reported.	n=1 in GT group has autistic trait. N=1 in HSCT group severe psychomotor retardation.	None in GT group, n=4 acute GVHD grade II in HSCT group.

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Appendices

Appendix 1 – Search Strategies

Key Question 1:

INCIDENCE LITERATURE

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE(R) Daily and MEDLINE(R)

11th October 2016

1	exp Severe Combined Immunodeficiency/
2	(severe adj combined adj (immuno-deficienc* or immunodeficienc*)).tw.
3	x-scid.tw.
4	((ada* or (adenosine adj deaminase*)) adj scid).tw.
5	or/1-4
6	incidence/ or prevalence/
7	(incidence or prevalence).tw.
8	6 or 7
9	5 and 8
10	exp Severe Combined Immunodeficiency/ep
11	9 or 10
12	limit 11 to humans

Embase 1974 to 2016 October 10

11th October 2016

1	exp severe combined immunodeficiency/
2	(severe adj combined adj (immuno-deficienc* or immunodeficienc*)).tw.
3	x-scid.tw.
4	((ada* or (adenosine adj deaminase*)) adj scid).tw.
5	or/1-4
6	incidence/ or prevalence/
7	(incidence or prevalence).tw.
8	6 or 7
9	5 and 8
10	exp severe combined immunodeficiency/ep [Epidemiology]
11	9 or 10
12	limit 11 to human

Key Question 2:

TREC SCREENING LITERATURE

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE(R) Daily and MEDLINE(R)

11th October 2016

1 exp Severe Combined Immunodeficiency/

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

3 x-scid.tw.

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

5 or/1-4

6 mass screening/ or neonatal screening/

7 screen*.tw.

8 exp Polymerase Chain Reaction/

9 polymerase chain reaction.tw.

10 pcr.tw.

11 (trec or trecs).tw.

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

13 or/6-12

14 5 and 13

15 exp Severe Combined Immunodeficiency/di

16 14 or 15

17 limit 16 to humans

Embase 1974 to 2016 October 10

11th October 2016

1 exp severe combined immunodeficiency/

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

3 x-scid.tw.

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

5 or/1-4

6 mass screening/ or newborn screening/

7 screen*.tw.

8 exp polymerase chain reaction/

9 polymerase chain reaction.tw.

10 pcr.tw.

11 (trec or trecs).tw.

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

13 or/6-12

14 5 and 13

15 exp severe combined immunodeficiency/di [Diagnosis]

16 14 or 15

17 limit 16 to human

Cochrane Library

11th October 2016

#1 MeSH descriptor: [Severe Combined Immunodeficiency] explode all trees

#2 (severe next combined next (immuno-deficienc* or immunodeficienc*)):ti,ab,kw

#3 x-scid:ti,ab,kw

#4 ((ada* or (adenosine adj deaminase*)) next scid):ti,ab,kw

#5 {or #1-#4}

Key Question 3:

NATURAL HISTORY WITH TREATMENT LITERATURE

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE(R) Daily and MEDLINE(R)

11th October 2016

1 exp Severe Combined Immunodeficiency/

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

3 x-scid.tw.

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

5 or/1-4

6 exp Anti-Infective Agents/

7 antibiotic*.tw.

8 exp Immunoglobulins/

9 immunoglobulin*.tw.

10 exp Stem Cell Transplantation/

11 (stem adj cell adj transplant*).tw.

12 exp Gene Therapy/

13 gene therapy.tw.

14 enzyme therapy/ or enzyme replacement therapy/

15 enzyme replacement therapy.tw.

16 adenosine deaminase/tu

17 or/6-16

18 5 and 17

19 exp Severe Combined Immunodeficiency/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]

20 18 or 19

21 limit 20 to humans

Embase 1974 to 2016 October 10

11th October 2016

1 exp severe combined immunodeficiency/

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

3 x-scid.tw.

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

5 or/1-4

6 exp antiinfective agent/

7 antibiotic*.tw.

8 exp immunoglobulin/

9 immunoglobulin*.tw.

10 exp stem cell transplantation/

11 (stem adj cell adj transplant*).tw.

12 exp gene therapy/

13 gene therapy.tw.

14 enzyme therapy/ or enzyme replacement therapy/

15 enzyme replacement therapy.tw.

16 adenosine deaminase/dt [Drug Therapy]

17 or/6-16

18 5 and 17

19 exp severe combined immunodeficiency/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]

20 18 or 19

21 limit 20 to human

Cochrane Library

11th October 2016

#1 MeSH descriptor: [Severe Combined Immunodeficiency] explode all trees

#2 (severe next combined next (immuno-deficienc* or immunodeficienc*)):ti,ab,kw

#3 x-scid:ti,ab,kw

#4 ((ada* or (adenosine adj deaminase*)) next scid):ti,ab,kw

#5 {or #1-#4}

Appendix 2 – Quality Assessment

Key Question 2: TREC Screening Studies

STARD checklist for the reporting of studies of diagnostic accuracy

Chien 2015

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	N/R
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#12
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#13
	4	Study objectives and hypotheses	#13
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#13 prospective
Participants	**6**	Eligibility criteria	#13
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	N/A
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#12 dates #13 location and setting
	9	Whether participants formed a consecutive, random or convenience series	#13 consecutive
Test methods	**10a**	Index test, in sufficient detail to allow replication	#13 clinical detection as index test
	10b	Reference standard, in sufficient detail to allow replication	#13
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	#15 clinical presentation
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	#13 TREC cut-offs, flow cytometry
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	N/R
	15	How indeterminate index test or reference standard results were handled	#13
	16	How missing data on the index test and reference standard were handled	N/R
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not carried out

	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	#14
	20	Baseline demographic and clinical characteristics of participants	#14
	21a	Distribution of severity of disease in those with the target condition	N/A
	21b	Distribution of alternative diagnoses in those without the target condition	#14 #15
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/R
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	N/R
	25	Any adverse events from performing the index test or the reference standard	N/R
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	N/R
	27	Implications for practice, including the intended use and clinical role of the index test	#15
OTHER INFORMATION			
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	N/R
	30	Sources of funding and other support; role of funders	N/R

Kwan 2013

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	#140 test specificity
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#140
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#141
	4	Study objectives and hypotheses	#141
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#141 prospective
Participants	**6**	Eligibility criteria	#141
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	N/A
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#141
	9	Whether participants formed a consecutive, random or convenience series	#141 consecutive
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	#150.e1

	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	N/A
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	#142
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	N/R
	15	How indeterminate index test or reference standard results were handled	#142
	16	How missing data on the index test and reference standard were handled	N/R
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not carried out
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	#150.e2
	20	Baseline demographic and clinical characteristics of participants	#141 #142
	21a	Distribution of severity of disease in those with the target condition	#142 #143
	21b	Distribution of alternative diagnoses in those without the target condition	#146
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	#148
	25	Any adverse events from performing the index test or the reference standard	N/R
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#149
	27	Implications for practice, including the intended use and clinical role of the index test	#148
OTHER INFORMATION			
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	N/R
	30	Sources of funding and other support; role of funders	#140

Kwan 2014

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	N/R

ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#729
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#730
	4	Study objectives and hypotheses	#730
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#730 prospective
Participants	**6**	Eligibility criteria	#730
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	N/A
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#730
	9	Whether participants formed a consecutive, random or convenience series	#730 consecutive
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	N/R
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	N/A
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	Supplementary material
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	N/R
	15	How indeterminate index test or reference standard results were handled	Supplementary material
	16	How missing data on the index test and reference standard were handled	N/R
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not carried out
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	N/R
	20	Baseline demographic and clinical characteristics of participants	#731 #732
	21a	Distribution of severity of disease in those with the target condition	#731
	21b	Distribution of alternative diagnoses in those without the target condition	#733
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or	N/A

		their distribution) by the results of the reference standard	
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	#734
	25	Any adverse events from performing the index test or the reference standard	N/R
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#735 #736
	27	Implications for practice, including the intended use and clinical role of the index test	#735 #736
OTHER INFORMATION			
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	N/R
	30	Sources of funding and other support; role of funders	#737

Kwan 2015

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	N/R
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#29
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#30
	4	Study objectives and hypotheses	#30
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#30 prospective
Participants	**6**	Eligibility criteria	#30
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	N/A
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#30
	9	Whether participants formed a consecutive, random or convenience series	#30 consecutive
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	#30
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	N/A
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	#30

	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	N/R
	15	How indeterminate index test or reference standard results were handled	#30
	16	How missing data on the index test and reference standard were handled	N/R
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not carried out
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	N/R
	20	Baseline demographic and clinical characteristics of participants	#31
	21a	Distribution of severity of disease in those with the target condition	#31 #32
	21b	Distribution of alternative diagnoses in those without the target condition	#31 #32
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	N/R
	25	Any adverse events from performing the index test or the reference standard	N/R
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#33
	27	Implications for practice, including the intended use and clinical role of the index test	#33
OTHER INFORMATION			
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	N/R
	30	Sources of funding and other support; role of funders	#33

Verbsky 2011

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	#82 specificity
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#82
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#83
	4	Study objectives and hypotheses	#83
METHODS			

Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#83 prospective
Participants	**6**	Eligibility criteria	#83
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	N/A
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#83
	9	Whether participants formed a consecutive, random or convenience series	#83 consecutive
Test methods	**10a**	Index test, in sufficient detail to allow replication	#84 Clinical detection
	10b	Reference standard, in sufficient detail to allow replication	#83
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	#84 clinical presentation
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	#83
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	N/R
	15	How indeterminate index test or reference standard results were handled	#83
	16	How missing data on the index test and reference standard were handled	N/R
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not carried out
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	N/R
	20	Baseline demographic and clinical characteristics of participants	#83
	21a	Distribution of severity of disease in those with the target condition	#84 #85
	21b	Distribution of alternative diagnoses in those without the target condition	#84 #85
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	#84
	25	Any adverse events from performing the index test or the reference standard	N/R
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#87
	27	Implications for practice, including the intended use and clinical role of the index test	#86 #87
OTHER			

INFORMATION			
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	N/R
	30	Sources of funding and other support; role of funders	#87

Vogel 2014

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	#289 positive predictive value
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#289 #290
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#290
	4	Study objectives and hypotheses	#290
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#290 prospective
Participants	**6**	Eligibility criteria	#290
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	N/A
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#290
	9	Whether participants formed a consecutive, random or convenience series	#290 consecutive
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	#290 #291
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	N/A
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	#291
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	N/R
	15	How indeterminate index test or reference standard results were handled	#291
	16	How missing data on the index test and reference standard were handled	N/R
	17	Any analyses of variability in diagnostic accuracy,	#291

		distinguishing pre-specified from exploratory	
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	#293
	20	Baseline demographic and clinical characteristics of participants	#292
	21a	Distribution of severity of disease in those with the target condition	#294 #295
	21b	Distribution of alternative diagnoses in those without the target condition	#294 #295 #297
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	#294
	25	Any adverse events from performing the index test or the reference standard	N/R
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#299 #300
	27	Implications for practice, including the intended use and clinical role of the index test	#297 #298
OTHER INFORMATION			
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	N/R
	30	Sources of funding and other support; role of funders	#300

Kanegae 2016

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	#375 sensitivity
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#374 #375
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#375
	4	Study objectives and hypotheses	#375
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#375 prospective
Participants	**6**	Eligibility criteria	#375
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	N/A
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#375 except dates that are N/R
	9	Whether participants formed a consecutive, random or convenience series	#375 consecutive

Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	#376
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	N/A
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	#376
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	N/R
	15	How indeterminate index test or reference standard results were handled	#376
	16	How missing data on the index test and reference standard were handled	N/R
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	#376
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	N/R
	20	Baseline demographic and clinical characteristics of participants	#376
	21a	Distribution of severity of disease in those with the target condition	#377
	21b	Distribution of alternative diagnoses in those without the target condition	#377
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	#376 #378
	25	Any adverse events from performing the index test or the reference standard	N/R
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#379
	27	Implications for practice, including the intended use and clinical role of the index test	#378
OTHER INFORMATION			
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	N/R
	30	Sources of funding and other support; role of funders	#379

Audrain 2014

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			

	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	No abstract
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	No abstract
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#137
	4	Study objectives and hypotheses	#137
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#137 prospective
Participants	**6**	Eligibility criteria	#137
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	N/A
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#137
	9	Whether participants formed a consecutive, random or convenience series	#137 consecutive
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	#137
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	N/A
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	#137
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	N/R
	15	How indeterminate index test or reference standard results were handled	#137
	16	How missing data on the index test and reference standard were handled	N/R
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	#137 #138
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	N/R
	20	Baseline demographic and clinical characteristics of participants	N/R
	21a	Distribution of severity of disease in those with the target condition	#137 #138
	21b	Distribution of alternative diagnoses in those without the target condition	#137 #138
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their	N/R

		distribution) by the results of the reference standard	
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	N/R
	25	Any adverse events from performing the index test or the reference standard	N/R
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#138
	27	Implications for practice, including the intended use and clinical role of the index test	#138
OTHER INFORMATION			
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	N/R
	30	Sources of funding and other support; role of funders	#138

Borte 2012

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	N/R
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#2552
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#2552
	4	Study objectives and hypotheses	#2552
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#2552 prospective
Participants	**6**	Eligibility criteria	#2552
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	N/A
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#2552
	9	Whether participants formed a consecutive, random or convenience series	#2552 consecutive
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	#2552 #2553
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	N/A
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-	#2553

		specified from exploratory	
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	N/R
	15	How indeterminate index test or reference standard results were handled	#2553
	16	How missing data on the index test and reference standard were handled	N/R
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not carried out
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	#2554
	20	Baseline demographic and clinical characteristics of participants	#2552
	21a	Distribution of severity of disease in those with the target condition	#2553
	21b	Distribution of alternative diagnoses in those without the target condition	#2553 #2554
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	N/R
	25	Any adverse events from performing the index test or the reference standard	N/R
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#2554
	27	Implications for practice, including the intended use and clinical role of the index test	#2554
OTHER INFORMATION			
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	N/R
	30	Sources of funding and other support; role of funders	#2555

Felipe 2016

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			N/R
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	
ABSTRACT			#70
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	
INTRODUCTION			#71
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#71
	4	Study objectives and hypotheses	

METHODS			#71 prospective
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#71
Participants	**6**	Eligibility criteria	N/A
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	#71
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#71 consecutive
	9	Whether participants formed a consecutive, random or convenience series	N/A
Test methods	**10a**	Index test, in sufficient detail to allow replication	#71
	10b	Reference standard, in sufficient detail to allow replication	N/A
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	#72
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	N/A
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/R
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	#72
	15	How indeterminate index test or reference standard results were handled	N/R
	16	How missing data on the index test and reference standard were handled	#72
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	N/A
	18	Intended sample size and how it was determined	
RESULTS			N/R
Participants	**19**	Flow of participants, using a diagram	#72
	20	Baseline demographic and clinical characteristics of participants	#72
	21a	Distribution of severity of disease in those with the target condition	#72 #73
	21b	Distribution of alternative diagnoses in those without the target condition	N/A
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/R
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	N/R
	25	Any adverse events from performing the index test or the reference standard	
DISCUSSION			#76
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#75
	27	Implications for practice, including the intended use and clinical role of the index test	

OTHER INFORMATION			N/R
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	#76
	30	Sources of funding and other support; role of funders	N/R

Acetta 2011

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	N/R
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#962
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#962 #963
	4	Study objectives and hypotheses	#963
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#962 #963 retrospective
Participants	**6**	Eligibility criteria	#963
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	#963
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#963
	9	Whether participants formed a consecutive, random or convenience series	#963 convenience
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	#963
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	N/A
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	#963
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	N/R
	15	How indeterminate index test or reference standard results were handled	#962
	16	How missing data on the index test and reference standard were handled	N/R

	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not carried out
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	N/R
	20	Baseline demographic and clinical characteristics of participants	#964
	21a	Distribution of severity of disease in those with the target condition	#964 #965
	21b	Distribution of alternative diagnoses in those without the target condition	#964 #965
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	N/R
	25	Any adverse events from performing the index test or the reference standard	N/R
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#966
	27	Implications for practice, including the intended use and clinical role of the index test	#966
OTHER INFORMATION			
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	N/R
	30	Sources of funding and other support; role of funders	#967

Adams 2014

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	#323 false positives
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#323
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#323 #324
	4	Study objectives and hypotheses	#324
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#323 #324 retrospective
Participants	**6**	Eligibility criteria	#324
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	#324
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#324
	9	Whether participants formed a consecutive,	#324 convenience

		random or convenience series	
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	#324 #325
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	N/A
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	#326
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	N/R
	15	How indeterminate index test or reference standard results were handled	#325
	16	How missing data on the index test and reference standard were handled	N/R
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not carried out
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	#325
	20	Baseline demographic and clinical characteristics of participants	#326
	21a	Distribution of severity of disease in those with the target condition	#326 #327
	21b	Distribution of alternative diagnoses in those without the target condition	#326 #327
	22	Time interval and any clinical interventions between index test and reference standard	N/A
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	N/R
	25	Any adverse events from performing the index test or the reference standard	N/R
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#329
	27	Implications for practice, including the intended use and clinical role of the index test	#238 #239
OTHER INFORMATION			
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	N/R
	30	Sources of funding and other support; role of funders	#239

Jilkina 2014

Section & Topic	No	Item	Reported on page #
TITLE OR			

ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	N/R
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	#324 #325
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	#325
	4	Study objectives and hypotheses	#325
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	#325 retrospective
Participants	**6**	Eligibility criteria	#325
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	#325
	8	Where and when potentially eligible participants were identified (setting, location and dates)	#325 #236
	9	Whether participants formed a consecutive, random or convenience series	#325 convenience
Test methods	**10a**	Index test, in sufficient detail to allow replication	N/A
	10b	Reference standard, in sufficient detail to allow replication	#327
	11	Rationale for choosing the reference standard (if alternatives exist)	N/A
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	N/A
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	#327
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	N/A
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	N/A
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	N/R
	15	How indeterminate index test or reference standard results were handled	#327
	16	How missing data on the index test and reference standard were handled	N/R
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	Not carried out
	18	Intended sample size and how it was determined	N/A
RESULTS			
Participants	**19**	Flow of participants, using a diagram	N/R
	20	Baseline demographic and clinical characteristics of participants	#328
	21a	Distribution of severity of disease in those with the target condition	#328
	21b	Distribution of alternative diagnoses in those without the target condition	#328
	22	Time interval and any clinical interventions between index test and reference standard	N/A

Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	N/A
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	N/R
	25	Any adverse events from performing the index test or the reference standard	N/R
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	#231
	27	Implications for practice, including the intended use and clinical role of the index test	#228 #230
OTHER INFORMATION			
	28	Registration number and name of registry	N/R
	29	Where the full study protocol can be accessed	N/R
	30	Sources of funding and other support; role of funders	N/R

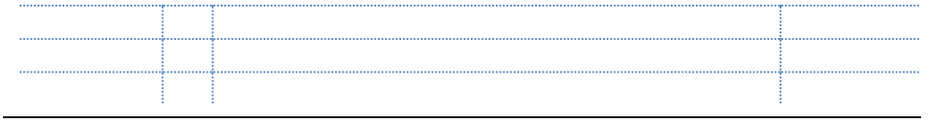

Table 30. Adapted CASP checklist summary for cohort studies for treatment studies.

Study	Clearly focused question	Acceptable cohort recruitment	Exposure accurately measured	Outcome accurately measured	Identification of confounds	Confounds taken into account	Follow-up complete	Follow-up long-enough	How precise are the results	Results fit with other studies
Dell Railey 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	N but differences explained
Sarzotti-Kelsoe 2009*	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Patel 2008	Y	Y	Y	Y	Y	Y	N/A	Y	Unclear	Y
Patel 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Gennery 2010	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y
Chan 2011	Y	N	N/R	Y	Y	Y	N	Unclear	N/R	Y
Brown 2011	Y	Y	Y	Y	Y	Y	Infections data unavailable 19/48 patients	Unclear	Y	
Bertrand 1999	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y
Giri 1994	Y	Y	Y	Y	Y	Y	N/A	N 14 months	Y	Y
Honig 2007	Y	Y	Y	Y	Y	Y	N/A	Y	N/R	Y
Mazzorali 2007	Y	Y	Y	Y	Y	Y	Y	Y	N/R	Y
Myers 2002	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y
Cipe 2012	Y	Y	Y	Y	Y	N	N/A	Unclear	N/R	Y

Study	Clearly focused question	Acceptable cohort recruitment	Exposure accurately measured	Outcome accurately measured	Identification of confounds	Confounds taken into account	Follow-up complete	Follow-up long-enough	How precise are the results	Results fit with other studies
Pai 2014	Y	Y	Y	Y	Y	Y	N/A	10 years	Y	Y
Neven 2009	Y	Y	N/R	Y	Y	Y	90/94	14 years	Y	Y
Rogers 2001	Y	Y	N/R	Y	Y	Y	N/A	Unclear	Y	Y
Slatter 2008	Y	Y	N/R	Y	Y	Y	Y	2 years	Y	Y
Titman 2008	Y	Y	N/R	Y	Y	Y	N	7 years	Y	N
Teigland 2013	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y
Wahlstrom 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Appendix 4 – NSC Criteria for appraising the viability, effectiveness and appropriateness of a screening programme

1. The condition

1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

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

3. 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.

2. The test

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

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

6. The test, from sample collection to delivery of results, should be acceptable to the target population.

7. 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.

8. If the test is for a particular mutation or set of genetic variants the method for their selection and the means through which these will be kept under review in the programme should be clearly set out.

3. The intervention

9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.

10. There should be agreed evidence based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.

4. The screening programme

11. 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" (such as Down's syndrome or 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.

12. 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.

13. The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.

14. 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 (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.

5. Implementation criteria

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

16. All other options for managing the condition should have been considered (such as improving treatment or providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

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

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

19. Evidence-based information, explaining the purpose and potential consequences of screening, investigation and preventative intervention or treatment, should be made available to potential participants to assist them in making an informed choice.

20. 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.