Newborn screening for severe combined immunodeficiency (SCID) in the NHS Newborn Blood Spot (NBS) screening programme: A rapid evidence review

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

Version: Final

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Contents

List of tables

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Plain English summary

When a new population screening programme is proposed in the United Kingdom (UK), it is assessed using the UK National Screening Committee (NSC) criteria for appraising its viability, effectiveness and appropriateness. The overall goal of population screening programmes is to provide early treatment or intervention to someone identified as being at higher risk of a condition before they have symptoms. Ideally this should lead to better outcomes than if the person were to present later with symptoms. In the UK, the current newborn screening programme looks for nine rare but serious conditions. Screening uses drops of blood, collected from an infant's heel onto a special card (also known as the 'heel prick test'). In the rare event that laboratory tests on this blood find an abnormal result, the child undergoes further testing to confirm whether or not they have one of the conditions screened for. If a child is then diagnosed with one of the conditions, they are referred for treatment.

Severe combined immunodeficiency (SCID) is a rare, inherited condition that results in low numbers of white blood cells and prevents the body from fighting infection properly. There are usually no symptoms of SCID when an affected baby is born, but if present the condition can develop very quickly and almost always results in death in the first year unless the child receives treatment. For this reason, a diagnosis of SCID is considered an emergency because the child needs urgent treatment. This usually involves haematopoietic stem cell transplantation (HSCT), also known as a bone marrow transplant. This transplant uses stem cells taken from a suitable donor (often a relative). These healthy, donated cells are then given to the child through an intravenous (IV) infusion. The stem cells travel to the bone marrow where they multiply over time. In this way, they can provide the child with a working immune system that is able to fight infection.

There is a test that can be used to screen for SCID, which involves counting the numbers of a specific product in the blood, called 'T-cell receptor excision circles (TRECs)'. TRECs are used to indicate how many working white blood cells of a particular type (T-cells) a person has. Below a certain number (cut-off point), the test result is considered abnormal (or 'positive'). However, it is important to note that the TREC test does not only identify SCID; a large number of other conditions that affect the immune system and result in very low levels of T-cells will also result in a positive TREC test.

The aim of this evidence summary was to assess evidence relevant to newborn screening for SCID published since the previous UK NSC evaluation. That evaluation, in 2017, concluded screening newborn babies for SCID should not be recommended because it was not known:

- how many healthy babies might receive an abnormal screening result (false positives)
- the best way to identify and care for babies with low numbers of white blood cells caused by other conditions
- how many affected babies were born into families who were already aware they may have SCID (for example, if a brother or sister already has the condition)
- how well laboratories would cope with the increase in testing and the presentation of more ill babies

The evidence looked promising, but more research was needed. The committee therefore recommended there should be a practical ‘in-service’ evaluation (ISE) of screening for SCID in English NHS services to answer some important questions. The ISE launched in September 2021 and completed in March 2024.

Like the 2017 review, the 2025 summary looked at evidence on the accuracy of the TREC test and the effectiveness of cell transplantation in treating babies identified by screening. In addition, the 2025 review also examined the acceptability of population screening for SCID to parents and carers of newborn babies.

The 2025 evidence summary has concluded that key areas of uncertainty remain over the best way to identify and care for babies with low numbers of white blood cells caused by other conditions. For many of these babies the treatment options remain limited, and the long-term outcomes unclear. The results from the ISE might be able to answer some of these questions when published.

In terms of acceptability, parents and carers generally supported newborn screening for SCID and the reporting of other conditions as a result of the test. They believed that early detection of non-SCID conditions was beneficial regardless of their treatability. However, this was mainly the opinion of parents and carers of babies who were healthy. The opinion of parents and carers of children who had a positive result for SCID, particularly those with a subsequent non-SCID diagnosis, was less clear. Further work may help to clarify this.

This evidence summary was commissioned by the UK NSC as part of its regular, scheduled reviews of existing recommendations and will form part of the evidence on which the Committee updates its recommendation, following analysis of the results of the ISE of screening for SCID in the English NHS).

Executive summary

Purpose of the review

The overall aim of this project was to summarise the available evidence relevant to newborn screening for severe combined immunodeficiency (SCID) in the National Health Service (NHS) newborn blood spot (NBS) screening programme. It provides an update to the previous evidence summary (completed in 2017) and includes evidence to inform one additional criterion, not considered by previous evidence summaries. This evidence summary was commissioned as part of a review of the evidence, by the United Kingdom (UK) National Screening Committee (NSC), following completion of an evaluation of screening for SCID in the English NHS.

Background

SCID is an inherited form of severe primary immune deficiency, which arises from mutations in at least 19 known genes and hence has a large number of subtypes. The proportions of different SCID subtypes vary widely geographically. SCID is characterised by T-cell lymphopenia (TCL), i.e. absence or significant reduction in the number of functioning T-cells. Hypomorphic mutations in SCID genes (mutations which result in reduced levels of activity of the gene product) result in particular forms of SCID known as atypical SCID and Omenn syndrome. Most subtypes of SCID have autosomal recessive inheritance.

SCID may be identified through screening, family history (cascade testing) or upon clinical presentation. SCID is usually asymptomatic at birth but presents in infancy as recurrent and frequently severe infections. In the absence of treatment, SCID is almost always fatal in the first year of life. Early identification of SCID is important, not only to enable prompt initiation of treatment, but also because children with the condition should not receive live vaccinations.

Immune reconstitution using allogeneic haematopoietic stem cell transplant (HSCT) is the primary treatment for SCID. Gene therapy may be an additional treatment option for some SCID sub-types.

The most widely used method of newborn screening for SCID involves the quantification of T-cell receptor excision circles (TRECs). TRECs are a deoxyribonucleic acid (DNA) by-product, generated during normal T-cell maturation; blood levels of TRECs are a surrogate marker of thymic output of newly formed T-cells, with an absence or low level of TREC being indicative of TCL. The TREC assay is performed using DNA extracted from a dried blood spot (DBS) sample and involves the use of polymerase chain reaction (PCR). The results from a TREC assay are indicative of the presence or absence of TCL, for which there are a large number of possible causes. TREC-based screening for SCID is, therefore, different from the other tests and target conditions included in the UK NHS NBS screening programme in that it is associated with high rates of incidental findings (screen positive results caused by conditions other than the target condition, SCID).

A report for the Health Information and Quality Authority, Republic of Ireland, published in 2023, examined the rates of SCID and non-SCID TCL detected by implemented screening programmes. The report found that the ratio of SCID to non-SCID TCLs detected by screening programmes ranged from 1:2 to 1:38. There is currently a lack of established consensus guidelines or algorithms for the management of non-SCID TCL cases detected through screening programmes for SCID.

Focus of the review

This evidence summary considered the evidence to inform four UK NSC criteria for a population screening programme. The criteria considered and the associated research questions were as follows:

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

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

Research question 1: What is the accuracy of the TREC test in population studies of screening for SCID?

Supplementary questions: What is the accuracy of the TREC test in subgroups: term babies, pre-term babies and sick babies? What is the rate and type of incidental findings (non-SCID TCL) observed in population screening for SCID?

Criterion 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.

Research question 2: Does HSCT (or gene therapy or thymic transplant, if appropriate) in SCID cases detected during the asymptomatic period lead to improved outcomes?

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

Research question 3: Is the experience of population screening for SCID acceptable to parents and carers of newborn babies?

In addition to summarising the available evidence to inform the above questions, this report includes:

- a set of vignettes describing conditions which may be detected as incidental findings from TREC-based screening for SCID
- an evidence map / horizon scanning document describing developments in gene therapy for SCID as an alternative or adjunct to HSCT
- a summary of the current newborn screening landscape for SCID, describing screening programmes and pilots currently in place both nationally and internationally

This evidence summary considers research published since the completion of the previous evidence review in 2017. However, because this review focused on previously identified evidence gaps, some of the inclusion criteria differed from those used by previous assessments. For this reason, new literature searches were conducted from 2011 to present, rather than relying upon updates to previous searches.

Recommendation under review

Based on the last UK NSC review of this condition that occurred in December 2017, the UK NSC does not recommend screening newborn babies for SCID. This was because it was not known:

- how many healthy babies may receive an abnormal screening result (false positives)
- the best way to identify and care for babies with low numbers of white blood cells caused by other conditions
- how many babies are born into families who are already aware they may have SCID (for example, if a brother or sister already has the condition)
- how well laboratories will cope with the increase in testing and the presentation of more ill babies

This evidence summary was commissioned by the UK NSC as part of its regular, scheduled reviews of existing recommendations.

Findings and gaps in the evidence of this review

Criterion 4 *(There should be a simple, safe, precise and validated screening test)*

The 2017 UK NSC evidence summary considered criterion 4 to be partially met. Data from existing screening programmes in the United States (US) and other countries included in this evidence summary is consistent with the findings of the 2017 UK NSC evidence summary; at the cut-off values needed to maintain high sensitivity, the TREC assay has poor positive predictive value (PPV) for SCID. There is some evidence, particularly from screening programmes in the US, that the use of screening algorithms that include repeat sampling (e.g. at term-adjusted gestational age) in preterm babies can markedly reduce false positive (FP) results due to transient TCL of prematurity. However, even where FP results due to prematurity are reduced or eliminated, the large number of other conditions that can give rise to a low TREC value (positive screening result) mean that the PPV for SCID remains consistently poor. There remains uncertainty about how the identification of non-SCID TCL conditions by screening should be handled, particularly where treatment options remain limited and long-term prognosis unclear. Whether or not criterion 4 is considered to be met is therefore likely to be substantially dependent upon how non-SCID TCLs (incidental findings) are treated.

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

The 2017 UK NSC evidence summary considered criterion 5 to be met. This evidence summary did not identify any new UK studies to inform research question 1. At the time of writing, the findings of the in-service evaluation (ISE) of newborn screening for SCID in the English NHS are not yet available. The evidence base available for inclusion in this report has, therefore, not changed since the previous UK NSC review.

Findings from the ISE may provide more up to date information on test and cut-off values from a large UK sample (criterion 5). The ISE also has the potential to provide UK-specific insights into how incidental findings have been handled in practice, including care pathways and outcomes for these children and their families (criterion 4).

Criterion 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)*

Publications included in this evidence summary provide information about the effect of diagnosing SCID through NBS screening on survival, and/or other outcomes following treatment with HSCT. The findings of these studies support the conclusion that diagnosis of SCID through NBS screening is associated with improvements in survival after treatment with HSCT. They strengthen the findings of the previous evidence review by directly assessing the effect of diagnosing SCID through NBS screening on survival and/or other outcomes following treatment and exploring the mechanisms underpinning this effect. We therefore consider that criterion 9 is met for screening-detected SCID. However, for many non-SCID conditions, treatment options remain limited and long-term prognosis unclear. Evaluating the harms and benefits resulting from screen detection of non-SCID conditions is a methodological challenge both for the non-SCID cases themselves and for gauging the balance of benefits and harms of NBS for SCID.

Criterion 6 *(The test, from sample collection to delivery of results, should be acceptable to the target population)*

This evidence summary found some evidence of parental support for NBS screening for SCID, primarily from studies connected to the pre-implementation pilot conducted in the Netherlands, as well as some evidence that parents regarded the early identification of non-SCID conditions (incidental findings) as advantageous irrespective of treatability, and there was support for reporting of such findings. However, the majority of evidence came from parents of healthy newborns, and there remains a paucity of evidence derived from parents who have experienced a positive result on NBS screening for SCID and in particular those who have experienced a positive screening result and a subsequent non-SCID diagnosis (incidental finding). There was also evidence of unmet needs around informed consent and provision of information and support following a positive NBS screening result. We therefore consider that, whilst there is some evidence of parental support for NBS screening for SCID and for the early identification of non-SCID conditions (incidental findings), further work (e.g. stakeholder dialogue and other directed Patient and Public Involvement activities) may be helpful to establish whether criterion 6 is met.

Recommendations on screening

The current published evidence base is not adequate to fully support implementation of NBS screening for SCID.

The findings of this evidence summary should be considered alongside findings from the ISE of newborn screening for SCID conducted in the NHS in England. As indicated, this could provide the information necessary to address some of the gaps identified in the published literature.

Further work is needed to explore how the identification of non-SCID TCL conditions by screening should be handled. It should be noted that there is no established methodology to guide the handling of incidental findings in the evaluation or study of screening programmes. In the current setting of NBS, the rarity of many of the non-SCID diagnoses exacerbates this problem. Any steps taken to address will be exploratory and the results are likely to be speculative rather than definitive. The vignettes on non-SCID diagnoses (Appendix 4) were developed to contribute to the discussion on the modelled estimate of screening's clinical and cost effectiveness. This is being undertaken as part of the ongoing ISE of NBS screening for

SCID. Stakeholder dialogue and Patient and Public Involvement activities may be helpful. In particular, the views of parents who have lived experience of a non-SCID (incidental) finding from NBS screening for SCID should be sought.

Limitations

The remaining uncertainty around how the identification of non-SCID TCL through screening should be handled is a key limitation. For many non-SCID TCL conditions, treatment options remain limited and long-term prognosis unclear.

This evidence summary employed standard systematic review methodology to ensure that the capture of relevant evidence was as complete as possible. In addition, to provide further context, this report includes vignettes of some non-SCID TCL conditions that may be identified by screening, a summary of the current status of NBS screening programmes for SCID internationally and findings from the results of horizon scanning for developments in gene therapy for SCID.

The systematic review component of this evidence summary was limited by a restriction to full publications in the English language.

Introduction and approach

Background

SCID is an inherited form of severe primary immune deficiency, which arises from mutations in at least 19 known genes and hence has a large number of subtypes. It is characterised by TCL, i.e. absence or significant reduction in the number of functioning T-cells.[1] Depending upon the genotype, SCID can also affect B cells and natural killer (NK) cells. Hypomorphic mutations in SCID genes (mutations which result in reduced levels of activity of the gene product) result in particular forms of SCID known as atypical SCID and Omenn syndrome. Most subtypes of SCID have autosomal recessive inheritance and there is an X-linked, recessive form of SCID that arises from mutations in the interleukin-2 receptor subunit gamma *(IL2RG*) gene. The proportions of different SCID subtypes vary widely geographically; e.g. the proportion of SCID cases accounted for by adenosine deaminase deficient SCID (ADA SCID) has been reported as 9.6% for the US, 11.6% for the Netherlands, 26.8% for the UK and 51.9% for the Republic of Ireland where 13 of the 14 ADA SCID cases in the sample were associated with Irish Traveller ethnicity.[1]

SCID may be identified through screening, family history (cascade testing) or upon clinical presentation. SCID is usually asymptomatic at birth and presents, in infancy, as recurrent and frequently severe infections (e.g. bacterial and viral infections such as *Streptococcus pneumoniae*, cytomegalovirus and adenoviruses, and opportunistic organisms such as *Pneumocystis jirovecii*), failure to thrive, persistent diarrhoea, and or oral thrush.[1] In the absence of treatment SCID is almost always fatal in the first year of life. Early identification of SCID is also important in the context of childhood immunisation; children with the condition should not receive live vaccines due to the potential for severe illness and mortality.

Immune reconstitution using allogeneic HSCT is the primary treatment for SCID.[1] Gene therapy may be an additional treatment option for some SCID sub-types (e.g. ADA SCID). ADA SCID is a subtype that is associated with neurological impairments not resolved by HSCT and which accounts for a relatively high proportion of SCID cases in the UK and Republic of Ireland.[2, 3]

The most widely used method of newborn screening for SCID involves the quantification of TRECs. The TREC assay is performed using DNA extracted from a DBS sample and involves the use of PCR. There are currently two commercially available TREC assay kits, the Revvity EnLite Neonatal TREC kit™ and the Immuno IVD SPOT-it™ screening kit, both of which are Conformité Européene (CE) marked. A previous evidence review, conducted for the UK N S C in 2017, included details of screening algorithms evaluated in prospective population studies and in studies with known retrospective positive samples.[4] A more recent assessment for the Health Information and Quality Authority (HIQA), Republic of Ireland, noted that (as at September 2022) newborn screening for SCID had been implemented in 7 European countries, the United States (US) and New Zealand, with regional or ongoing implementation, piloting or assessment being noted in 9 further countries including Canada and the UK; the majority of programmes used TREC-based screening, with 4 countries using combined TREC- and kappa-deleting excision circles (KREC)-based screening. The HIQA review included a summary of the current newborn screening landscape for SCID, describing screening programmes and pilots currently in place both nationally and internationally.[1] Our evidence review includes an update to this summary (Appendix 6).

TRECs are a DNA by-product, generated during normal T-cell maturation; blood levels of TRECs are a surrogate marker of thymic output of newly formed T-cells, with an absence or low level of TREC being indicative of TCL. Originally developed to assess thymic output in relation to aging and human immunodeficiency viruses (HIV) infection, the TREC assay has been adapted for use in newborn screening. In this context, it is important to note that the results from a TREC assay are indicative of the presence or absence of TCL, for which there are a large number of possible causes and are not specific for SCID. TREC-based screening for SCID is, therefore, different from the other tests and target conditions included in the UK NHS NBS screening programme (sickle cell disease, cystic fibrosis, congenital hypothyroidism and 6 inborn errors of metabolism)[5] in that it is associated with high rates of incidental findings (screen positive results caused by conditions other than the target condition, SCID).

Both the 2017 evidence review, conducted for the UK NSC,[4] and the HIQA Ireland report,[1] reported data on the numbers of cases of non-SCID TCL reported in published studies of TREC-based screening. Both of these reports also included some estimates of the overall incidence of non-SCID TCLs, by reported screening programme, but did not report estimates of the incidence of individual non-SCID TCL conditions. Overall incidence of non-SCID TCL, reported in the 2017 evidence review, were for individual states in the US and were derived from a single publication;[6] reported incidence of non-SCID TCL ranged from 1 in 32,000 (California) to 1 in 2,100 (Michigan). The HIQA Ireland report provided data on the overall incidence of non-SCID TCL (excluding pre-term birth) and included the same US data, as well as additional data for Catalonia, Spain (1 in 10,510),[7] Sweden (1 in 4,135),[8] and Israel (1 in 6,565).[9] The report noted that data provided by these studies indicated that the ratio of SCID to non-SCID TCLs detected by screening programmes ranged from 1:2 to 1:38.[1] In addition, the HIQA Ireland report listed 21 non-SCID congenital conditions that may result in an abnormal TREC result at screening: 22q11.2 Deletion Syndrome (DiGeorge syndrome); combined immunodeficiency (CID); ataxia telangiectasia (A-T); dedicator of cytokinesis 8 (DOCK 8) deficiency; anhidrotic ectodermal dysplasia with immune deficiency; Trisomy 21; Trisomy 18; Kabuki syndrome; CHARGE syndrome; Noonan syndrome; Jacobsen syndrome; Fryns syndrome; CLOVES syndrome; Renpenning syndrome; thrombocytopenia-absent radius (TAR) syndrome; vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities (VACTERL) syndrome; Dandy Walker syndrome; Barth syndrome; Schimke immuno-osseous dysplasia; cartilage hair hypoplasia; cytogenetic abnormalities.[1] The report also identified 8 secondary causes for low TREC values: prematurity (typically TCL in those born before 37 gestational weeks which progressively normalises over time); congenital heart disease; chylothorax; gastrointestinal anomalies; vascular leakage; hydrops; neonatal leukaemia; maternal causes (such as autoimmune disease, HIV infection, and immunosuppression).[1]

The rate and diversity of incidental findings is likely to complicate the process of obtaining informed consent for TREC-based screening for SCID in that it may be argued that a truly informed parent should be aware of the purpose and process of screening, as well as all possible outcomes of the screening test and their subsequent impact (e.g. further testing, treatment options, potential for identification of untreatable conditions). A recent systematic review of the acceptability of blood spot screening and genome sequencing in newborn screening, conducted for the UK NSC,[10] included one study of newborn screening for SCID.[11] However, this review only considered assessments of acceptability that were made antenatally or within 1 month of birth and may therefore not have captured potential effects on parental attitudes of the unique aspects of TREC-based screening for SCID described above. Our evidence review considered, specifically, studies which examine the acceptability of screening

for SCID and also included studies that assess acceptability at later time points and/or retrospectively.

Two recent US publications noted the absence of established consensus guidelines or algorithms for non-SCID TCL cases detected through screening programmes for SCID,[12, 13] and the review of international screening programmes for SCID, included in the HIQA Ireland report, also identified no clinical guidelines or pathways. Our report includes a series of vignettes of causes of non-SCID TCL, specified by the UK NSC (Appendix 4); these vignettes were informed by condition-specific searches and include details of any clinical guidelines identified as well as findings from horizon scanning searches to identify any emerging novel treatments.

Current policy context and previous reviews

Newborn screening for SCID is not currently recommended in the UK.[14] The UK NSC reviewed the evidence for newborn screening for SCID, against its programme appraisal criteria, in 2012[15] and updated this review in 2017.[4, 16] An ISE of newborn screening for SCID is ongoing in English NHS services and was due to complete in March 2024.[17] A more recent (2023) Health Technology Assessment (HTA) has been conducted by HIQA Ireland.[1] However, this assessment was conducted in the context of a pre-existing, tandem mass spectrometry-based screening programme for ADA SCID (implemented in Ireland in May 2022) and is, therefore not directly applicable to the UK context. The accumulation of metabolic substrates associated with ADA SCID is detectable in DBS samples using tandem mass spectrometry, a method that is already used in both the UK and Republic of Ireland NBS screening programmes to screen for a number of different inborn errors of metabolism and which does not result in the high rates of incidental findings associated with TREC-based screening; more than half of SCID cases in the republic of Ireland are ADA SCID and can be detected using tandem mass spectrometry-based screening. Tandem mass spectrometry cannot be used to screen for other forms of SCID.

This evidence summary provides an update to the 2017 UK NSC review,[4] and focuses on UK NSC criteria for a population screening programme,[18] which were deemed to be not fully met following the 2017 review:

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

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

Criterion 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.

This evidence summary has also considered one additional criterion, not examined by previous evidence reviews:

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

Because our review focused on previously identified evidence gaps, some of our inclusion criteria (particularly in relation to acceptability) differed from those used by previous assessments. For this reason, new literature searches were conducted from 2011 to present, rather than relying upon updates to previous searches.

Objectives

The overall aim of this project was to summarise the available evidence relevant to newborn screening for SCID in the UK NHS NBS screening programme. The following research questions were defined to address specific project objectives:

1. What is the accuracy of the TREC test in population studies of screening for SCID?
    - What is the accuracy of the TREC test in subgroups: term babies, pre-term babies and sick babies?
    - What is rate and type of incidental findings (non-SCID TCL) observed in population screening for SCID?
2. Does HSCT (or gene therapy or thymic transplant, if appropriate) in SCID cases detected during the asymptomatic period lead to improved outcomes?
    - Detection in the asymptomatic period might include universal newborn screening, familial cascade detection or individuals detected by other means
3. Is the experience of population screening for SCID acceptable to parents and carers of newborn babies?
    - Studies of the acceptability of screening for SCID, assessed pre-screening, during the screening phase and post-screening, were considered

In addition to summarising the available evidence to inform the above questions, our report includes:

- a set of vignettes describing conditions which may be detected as incidental findings from TREC-based screening for SCID
- an evidence map/horizon scanning document describing developments in gene therapy for SCID as an alternative or adjunct to HSCT
- a summary of the current newborn screening landscape for SCID, describing screening programmes and pilots currently in place both nationally and internationally

Table 1: Key questions for the evidence summary and relationship to the UK NSC screening criteria

Criterion	Key questions	Studies Included
Screening Test		

	Criterion	Key questions	Studies Included
4	There should be a simple, safe, precise and validated screening test.	What is the accuracy of the TREC test in population studies of screening for SCID?	11[19-29]
5	The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.	What are the types and rates of incidental findings (non-SCID TCL) in NBS screening for SCID?	
Treatment			
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.	Does HSCT (or gene therapy or thymic transplant, if appropriate) in SCID cases detected during the asymptomatic period lead to improved outcomes?	3[30-32]
Acceptability			

	Criterion	Key questions	Studies Included
6	The test, from sample collection to delivery of results, should be acceptable to the target population.	Is the experience of population screening for SCID acceptable to parents and carers of newborn babies?	6[11, 33-37]

HSCT: haematopoietic stem cell transplantation; NBS: newborn blood spot; SCID: severe combined immunodeficiency; TCL: T-cell lymphopenia; TREC: T-cell receptor excision circle

Methods

The current review was conducted by Kleijnen Systematic Reviews Ltd (KSR), in keeping with the UK NSC evidence review process.

All searching was undertaken to the highest standard to meet best practice requirements recommended by the Centre for Reviews and Dissemination (CRD) and the Cochrane Collaboration Handbook.[38, 39]

A sensitive search strategy was developed to retrieve references to studies on screening for and the treatment of SCID. Search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches combined relevant search terms comprising indexed keywords (e.g. Medical Subject Headings (MeSH) and EMTREE) and free text terms appearing in the title and/or abstract of database records. Search terms were identified through discussion with the review team, by scanning background literature and ‘key articles’ already known to the review team, and by browsing database thesauri.

The identification of references on screening for and the treatment of SCID required a multi-faceted approach to the structure of the search strategy. Relevant synonyms for the SCID population were separately combined with screening terms and with the relevant treatment terms as follows:

(SCID *AND* screening)

OR

(SCID *AND* treatment)

Only studies conducted in humans were sought. Searches were not limited by language or by publication status (unpublished or published). In order to maintain relevance to current clinical practice and update existing research, searches were date limited from 2011 to present. Conference proceedings and preprints were not included in the search.

All searches were independently peer reviewed by a second KSR information specialist. Strategy peer review was informed by items based on the Canadian Agency for Drugs and Technologies in Health (CADTH) checklist.[40, 41]

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling. Individual records within the EndNote libraries were tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme, or search question. This enabled the information specialist to track the origin of each individual database record, and its progress through the screening and review process.

Eligibility for inclusion in the review

The process for selecting studies for inclusion in this evidence review was as follows:

1. Each title and abstract was reviewed against the inclusion/exclusion criteria by two reviewers, independently. Any disagreements were resolved by discussion and consultation with a third reviewer, as needed.
2. Full-text articles required for the full-text review stage were acquired.
3. Each full-text article was reviewed against the inclusion/exclusion criteria by two reviewers, independently, to determine whether the article was relevant to one or more of the review questions. Any disagreements were resolved by discussion and consultation with a third reviewer, as needed.

Eligibility criteria for each question are presented in Table 2 below. Studies published in languages other than English were excluded. Only studies reported in peer reviewed publications were eligible for inclusion; conference abstracts were excluded.

Table 2: Inclusion and exclusion criteria for the key questions

Key question	Inclusion criteria							Exclusion criteria
	Population	Target Condition	Intervention	Reference standard	Comparator	Outcome	Study type	
1. Screening test	Newborns Subgroups of interest: • term babies • pre-term babies • sick babies	SCID	PCR-based measurement or TREC in dried blood spots.	Flow cytometry, genetic testing and/or subsequent clinical detection of SCID.	N/A	Sensitivity, specificity, PPV, NPV, of the intervention (by screening test, e.g. test kit used, and threshold) for the target condition SCID. Incidental findings (type and incidence of non-SCID TCL).	Studies in randomly assigned or consecutively enrolled populations (diagnostic cohort studies). Diagnostic case-control studies were also considered.	None
2. Treatment	Newborns, infants or children with SCID.	N/A	Treatment (HSCT, gene therapy or thymic transplant) where:	Treatment (HSCT, gene therapy or thymic transplant) where:	N/A	Survival, safety (e.g. incidence of AE associated with HSCT), freedom from	Any comparative study design, in humans.	None

			1. SCID has been detected through population screening 2. SCID has been detected early (e.g. incidentally or through cascade testing) 3. SCID which remains symptom-free (could include both screening-detected and early-detected	1. SCID has been detected without population screening 2. SCID has been detected late 3. SCID has been detected following the development of symptoms		immunoglobulin substitution (with consideration to the potential confounding factors related to treatment and complications), CD3+ T-cell and IgA recovery, cognitive behavioural or neurological outcomes.		
3. Acceptability	Parents and carers of newborns/infants or children to whom SCID screening was offered.	SCID	Newborn population screening programme for SCID.	Current offer and delivery of newborn population screening programme for SCID (as suggested to the screening programme that it is examined).	N/A	Overall: • Stated parental acceptability/perceptions of screening	RCTs, cohort studies, feasibility studies, mixed methods studies, surveys and/or focus groups, qualitative in-	None

		Parents or carers characteristics of acceptability/experience including: • logistic measures of acceptability (e.g. convenience, accessibility) • procedure related measures of acceptability (e.g. pain/physical discomfort for the baby, information confidence in result) • psychosocial measures of acceptability (e.g. anxiety, fit with values) • knowledge related measures (e.g. understandi	terview studies, systematic reviews

			ng of the intervention and its effectiveness)	

AE: adverse events; CD3+: cluster of differentiation 3 positive; HSCT: haematopoietic stem cell transplantation; IgA: immunoglobulin A; N/A: not applicable; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; RCTs: randomised controlled trials; SCID: severe combined immunodeficiency; TCL: T-cell lymphopenia; TREC: T-cell receptor excision circle

Data extraction

Data was extracted by one reviewer, using piloted data extraction forms. A second reviewer checked data extraction and any disagreements were resolved by consensus or discussion with a third reviewer.

Appraisal for quality/risk of bias tool

The methodological quality of included studies was assessed by one reviewer and checked by a second reviewer; any disagreements were resolved by discussion or by consultation with a third reviewer. A summary of risk of the methodological quality of included studies is provided in the question level synthesis and full risk of bias assessments, for each study, are provided in Appendix 3.

The following tools were used to assess the quality and risk of bias of each study included in the review:

- studies which reported accuracy of TREC-based screening for SCID, or from which accuracy outcomes were calculated: Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool[42]
- studies which used multivariable modelling to explore the factors associated with post-treatment outcome in patients with SCID: Quality In Prognosis Studies (QUIPS) tool[43]
- observational studies which used simple pairwise comparisons to explore the factors associated with post-treatment outcome in patients with SCID: Modified Critical Appraisal Skills Programme (CASP) checklist for cohort studies of treatment, as used in the previous UK NSC evidence summary (Leaviss et al. 2017)[4]
- quantitative and qualitative studies reporting acceptability data: Mixed Methods Appraisal Tool (MMAT)[44]

Methods of analysis/synthesis

A narrative synthesis of results is presented, structured by UK NSC criterion and key question. No meta-analyses were conducted.

Databases/sources searched

Search strategies were developed to identify studies on newborn screening for SCID, as recommended in the CRD guidance for undertaking reviews in health care[38] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[45]

Candidate search terms were identified from target references, browsing database thesauri (e.g. MEDLINE MeSH and Embase EMTREE), existing reviews and initial scoping searches. Strategy development involved an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies were developed specifically for each database and the keywords and thesaurus terms were adapted according to the configuration of each database.

In order to maintain relevance to current clinical practice and update existing research, all searches were date limited from 2011 to present.

The following databases were searched on 16 to 17 April 2024 for relevant research on SCID:

- MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily (Ovid): 1946 to April 15, 2024
- EMBASE (Ovid): 1974 to 2024 April 16
- CINAHL (EBSCO): 2011 to 16.4.24
- PsycINFO (Ovid): 1806 to April Week 1 2024
- Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 4 of 12, April 2024
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 3 of 12, March 2024
- International HTA Database (Internet) (https://database.inahta.org/): 2011 to 16.4.24
- KSR Evidence (Internet) (https://ksrevidence.com/): 2011 to 16.4.24

Additional searches

Searches of the following resources were conducted on 8 May 2024 to identify the latest background, guideline and policy documents on gene therapy for SCID and to present a series of vignettes in the fields of DiGeorge syndrome, ataxia telangiectasia, DOCK8 immunodeficiency syndrome, congenital athymia and cartilage hair hypoplasia (CHH).

In order to identify only the most recent research, these searches were date limited from 2017 to present.

- Trip Database (Internet) (https://www.tripdatabase.com/): 2017 to 8.5.24
- Guidelines International Network (GIN) (Internet) (https://g-i-n.net/international-guidelines-library/): 2017 to 8.5.24
- National Institute for Health and Care Excellence (NICE) (Internet) (https://www.nice.org.uk/): 2017 to 8.5.24
- National Institute for Health and Care Research (NIHR) HTA (Internet) (https://www.nihr.ac.uk/): 2017 to 8.5.24
- ECRI Guidelines Trust (Internet) (https://guidelines.ecri.org/): 2017 to 8.5.24
- Policy Commons (Internet) (https://policycommons.net/): 2017 to 8.5.24
- ScanMedicine (Internet) (https://scanmedicine.com/): 2017 to 8.5.24
- Orphanet Newborn Screening Bibliographical Knowledgebase (Internet) (https://nbs.orphanet.app/): 2017 to 8.5.24

The following trials registers were searched on 29 May 2024 and 8 July 2024 to identify any potentially relevant ongoing research:

- ClinicalTrials.gov (Internet) (https://clinicaltrials.gov/): 2017 to 29.5.24; 2017 to 8.7.24
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (Internet) (https://trialsearch.who.int/): 2017 to 29.5.24; 2017 to 8.7.24
- European (EU) Clinical Trials Register (Internet) (https://www.clinicaltrialsregister.eu/): 2017 to 29.5.24; 2017 to 8.7.24

Full strategies for all searches are provided in Appendix 1.

The main Embase strategy for each search was independently peer reviewed by a second information specialist based on the CADTH Peer Review checklist.[40]

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling. Individual records within the EndNote libraries were tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enabled the information specialist to track the origin of each individual database record, and its progress through the screening and review process.

Overview of included studies

The literature searches conducted for this evidence review identified 2,550 unique publications, after deduplication. Following initial screening of titles and abstracts, 112 publications were considered to be potentially relevant and ordered for full paper screening; of these, 21 are included in the Question level synthesis.[11, 19-37, 46]

Twelve publications provided data to inform research question 1,[19-29, 46] 3 publications provided data to inform research question 2[30-32] and 6 publications provided data to inform research question 3.[11, 33-37]

A further 23 publications met the inclusion criteria for this review and had previously been included in either the 2017 evidence review for the UK NSC,[47, 48] the Republic of Ireland HIQA report,[7-9, 13, 49-61] or both;[6, 62-64] previously extracted data from these studies were not re-extracted for the current evidence summary.

Appendix 2 provides a Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart for this evidence summary and details of studies included and excluded after full text screening.

Question level synthesis

Criteria 4 and 5 — Accuracy of the screening test

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

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

Questions to inform criteria 4 and 5 were included in the 2017 UK NSC evidence review.[4] The 2017 UK NSC evidence review concluded that criterion 5 was met and that criterion 4 was partially met.

Question 1 — What is the accuracy of the TREC test in population studies of screening for SCID?

The 2017 UK NSC evidence review considered this question. One of the studies included in the 2017 UK NSC evidence review (Adams et al. 2014)[65] evaluated a commercial TREC assay (EnLite™ Neonatal TREC kit, Perkin Elmer) to assess its suitability for NBS screening for SCID in the UK. Adams et al. 2014 evaluated 5 different TREC cut-off values using over 5,000 normal DBS samples from the regional newborn screening laboratory, Great Ormond Street Hospital (GOSH), UK and DBS samples from 18 known SCID positive cases. The presumptive positive rate, reported by Adams et al. 2014, ranged from 0.04% using a cut-off value of 20 copies/µL to 1% using a cut-off value of 40 copies/µL.[65] The 2017 UK NSC evidence review concluded that data from Adams et al. 2014 could be used to define a suitable cut-off for a UK screening and hence that criterion 5 was met.[4]

With respect to criterion 4, the 2017 UK NSC evidence review concluded that, although there was evidence to support high sensitivity values for TREC assays for the target condition SCID, positive predictive values (PPVs) were poor.[4] It was noted that, even when low TREC cut-off values are used, the test identifies newborns with other (non-SCID) TCLs where treatment options may be limited and/or long-term prognosis unclear, and that false positive (FP) results also occur in pre-term babies. The 2017 UK NSC evidence review therefore considered that criterion 4 was partially met.[4]

What is added by this evidence review

This evidence review provides an updated summary of the published studies available to inform question 1, which includes recent publications reporting experience from established national and state-level (US) screening programmes and screening pilots.

The inclusion criteria for this evidence summary (Table 2) specified the consideration of the performance of TREC assays in relevant subgroups (pre-term babies, sick babies and term babies), as well as data on the types and incidence of non-SCID TCLs identified by newborn screening.

In addition to the systematic literature review, this evidence summary includes a series of vignettes of some of the non-SCID congenital conditions that can be identified by TREC-based screening (Appendix 4). The current state of knowledge in respect of the aetiology, epidemiology, diagnosis and management of these conditions is summarised in these vignettes.

Description of new evidence in relation to previous evidence reviews

The searching and title and abstract screening stages of the evidence review were conducted as a single process, with consideration of all three research questions. Appendix 2 provides an overall PRISMA flow chart for this evidence summary and details of studies included and excluded after full text screening.

Following full text screening, there were 32 publications that met the inclusion criteria specified for research question 1. Twenty publications[6-9, 13, 47-55, 57-62] were included in a previous evidence review about the addition of TREC-based screening for SCID to an NBS screening programme (the 2017 UK NSC evidence review [4] or Republic of Ireland HIQA report[1]). Publications previously included in these evidence reviews are not reported here.

Twelve new publications, which provided data to inform question 1, are included in this evidence summary.[19-29, 46] Two of these publications reported results from state-level screening programmes in the US.[20, 27] One publication provided an updated, larger data set for the state of California;[27] earlier data for California was reported in publications included in previous evidence reviews.[6, 47, 48] The second publication provided data for a new state, Arizona,[20] for which data had not previously been published individually and which was not included in the combined report of data from ten states plus the Navajo Nation, which was included in both previous evidence summaries.[6] A further publication[24] provided an updated, larger data set for the screening programme in Israel; earlier data from the Israel screening was reported in one publication[9] included in Republic of Ireland HIQA report.

Overall, 9 of the publications included in this section were retrospective reports of experience from implemented TREC-based NBS screening programmes for SCID.[19, 20, 22-25, 27-29] The 3 remaining publications reported prospective pilot evaluations of TREC-based NBS screening for SCID.[21, 26, 46]

Retrospective reports of experience from implemented screening programmes

All 9 publications in this group were reports of experience following the addition of TREC-based screening for SCID to an existing NBS screening programme.[19, 20, 22-25, 27-29] Implementation of screening for SCID occurred between 2010 (California, USA)[27] and 2020 (Denmark)[19] and the time periods for which screening experience was reported ranged from the first year of implementation to the first 7 years.

All of the reported screening programmes used real-time (RT)-PCR based TREC quantification methods and one programme (Japan)[29] also measured KREC. Where reported, the majority of screening programmes used commercial assay kits; 3 programmes (Denmark,[19] New Zealand[23] and Singapore[22]) used EONIS™ PCR kit (Perkin Elmer, Turku, Finland), 3 programmes (Japan,[29] Israel and US, California[27]) used EnLite™ Neonatal TREC kit (Perkin Elmer, UK), and the German programme used EnLite™ Neonatal TREC kit (Perkin Elmer, Finland) in 3 laboratories, SPOT-it™ (ImmunoIVD, Sweden) in 5 laboratories and in-house platforms in 3 laboratories.[28] All publications described screening programmes which incorporated some form of repeat testing, involving re-analysis of the same DBS sample, repeat sampling and analysis from the same DBS and/or collection and analysis of a new DBS sample. There was some variation in the TREC cut-off values used, however, all repeat test cut-offs were in the range <19 copies/μL to <31 copies/μL; <19 copies/μL was the most commonly used cut-off (4/9 screening programmes).[20, 22, 23, 27] Six screening programmes incorporated separate urgent referral for absent or very low TREC results.[20, 22, 23, 27-29] A summary of the TREC-based NBS

screening strategies for SCID, used in implemented screening programmes, is provided in Table 3 and flow charts of screening algorithms are included in Appendix 6.

All screening test performance and screening outcomes were reported for the whole newborn screened population; none of the studies identified by this evidence review reported separate data for the specified subgroups of interest (pre-term babies, sick babies and term babies). Two publications, reporting the screening programmes in Japan[29] and Singapore,[22] provided the proportion of screened newborns who were full term (98.34% and 92.4%, respectively). Although no separate data was reported for screening test performance in pre-term or sick babies, six publications described screening programmes where the screening algorithm incorporated collection and analysis of a second, later DBS sample for preterm/low birth weight[19, 20, 22, 23, 25] or sick (cared for in neonatal intensive care unit [NICU])[27] babies with an initially abnormal TREC result. Where reported, rates of repeat testing, including new sample requests, were consistently low (≤1%). Where reported or estimable, the sensitivity of screening programmes was consistently high. Three reports of screening experience[20, 23, 24] stated that no additional cases of SCID (not detected by screening) were identified during the study period, i.e. there were no known false negative (FN) screening results and sensitivity was assumed to be 100%. One further publication[27] reported a finding of 2 cases of SCID that were negative at NBS screening (FN), giving a sensitivity of 96%; however, it was noted that both were cases of late-onset SCID. The remaining five reports of screening experience did not provide any information about whether or not any additional (not detected by screening) cases of SCID had been identified.[19, 22, 25, 28, 29] Calculated PPVs for SCID of TREC-based NBS screening varied widely, ranging from 1.54% (95% confidence interval [CI]: 1.30% to 1.82%) for Japan[29] to 25.93% (95% CI: 18.42% to 35.17%) for Arizona, US.[20] Calculated PPVs for TCL were higher, ranging from 34.64% (95% CI: 29.40% to 40.29%) to 81.48% (95% CI: 64.48% to 91.36%). A summary of screening performance, based on reported experience is provided in Table 4.

TREC-based NBS screening for SCID resulted in detection of cases of non-SCID TCL, in addition to SCID cases. Publications of screening experience reported a wide variety of syndromic and non-syndromic causes of non-SCID TCL. Overall, reports from implemented screening programmes indicated that the rate of detection of non-SCID TCL was consistently higher (more than double) the rate of detection of SCID. The most commonly identified syndromic causes of non-SCID TCL were 22q11.2 DS (found by all publications which reported details)[20, 22-24, 27-29] and trisomy 21 (found by all but one of these publications).[20, 22, 24, 27-29] Cases of coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities (CHARGE) syndrome were recorded in 3 publications,[23, 28, 29] and 2 publications recorded cases of A-T.[27, 28]

The numbers of reported cases of TCL of prematurity were generally highest in those screening programmes which did not include use of a repeat sample in premature babies with initially abnormal TREC results (16/105 screen-positive results, Israel[24], 7/78 screen-positive results, Japan[29]). Data from screening programmes in the US indicated that in Arizona,[20] where repeat sampling at term-adjusted gestational age is requested for all preterm newborns with an initially abnormal TREC result, repeat sampling resulted in normalisation of the TREC result (i.e. a screen negative result) in all 75 cases, and although the report of the California screening programme[27] reported 33 cases of transient TCL of prematurity, this publication also noted that T-cell counts rose to normal levels in all premature infants as they approached full term. In the Singapore screening programme, repeat sampling was requested for preterm (<32 weeks) newborns who had a birth weight of <1,500 g and an initially abnormal TREC result in the range 4-18 copies/μL (all TREC results <4 copies/μL were classified as urgent screen-positives); this strategy resulted in normalisation of TREC results in 7/9 cases.[22] The screening algorithm

implemented in New Zealand includes the scheduling of repeat sampling for low birth weight (≤1,500 g) newborns with initially abnormal TREC results; this strategy resulted in normalisation of TREC results in 34/48 cases.[23] The publications describing the screening programmes in Denmark[19] and Taiwan[25] both reported the use of algorithms that incorporated repeat sampling for premature babies with initially abnormal TREC results, but neither publication reported data to inform the effects of repeat testing.

Details of reported screening outcomes are provided in Table 5.

Prospective pilot studies

Three publications reported prospective pilot evaluations of TREC-based NBS screening for SCID in Ukraine,[21] Bulgaria.[26] and Russia.[46]

A 21-month pilot study to evaluate the addition of screening for primary immunodeficiencies to the Ukraine NBS screening programme was commenced in May 2020. The existing screening programme utilises DBS samples from heel pricks; during the pilot study, an additional DBS was collected for SCID screening. Screening, in the pilot study, was based on determination of TREC/KREC levels using a proprietary RT-PCR method (Scientific Medical Genetic Center LeoGENE, Ltd, Lviv, Ukraine). The initial threshold for an abnormal TREC/KREC result was <5,000 copies per 10^6 cells in the first 4,833 newborns screened, decreased to <2,000 copies per 10^6 cells for the remaining 5,517 newborns screened. The screening algorithm included retesting of samples with abnormal results and repeat sample testing for babies with persistently abnormal results; absent or very low (<100 copies per 10^6 cells) TREC values were classified as urgent abnormal. When the cut-off value of 5,000 copies per 10^6 cells was used, the retest rate was 7.6% and the repeat sample rate was 0.9%.[21] When the cut-off was lowered to 2,000 copies per 10^6 cells, the retest rate fell to 4.1% and the repeat sample rate to 0.5%.[21] The pilot included all babies, born in the Ternopil region of Western Ukraine, who participated in the established NBS screening programme during the study period.[21] During the pilot, 1 case of SCID (unknown genetic cause) was identified with absent TREC and normal KREC, and 1 case of transient TCL of prematurity was identified with a TREC value <5,000 copies per 10^6 cells and normal KREC.[21]

The second publication reported limited details of a pilot study conducted to evaluate the addition of TREC and KREC testing for SCID to the current NBS screening programme in Bulgaria. The study included 2,228 NBS samples collected between December 2019 and April 2021 and used RT-PCR-based TREC quantification with the EnLite™ Neonatal TREC kit (Perkin Elmer, UK) and a cut-off of ≤36 copies/μL.[26] Abnormal tests were repeated in duplicate and no repeat sample step was reported.[26] The retest rate was 42/2,228 (1.89%) and the presumed positive rate was 8/2,228 (0.36%); details of screening outcomes (diagnoses) were not reported.[26]

The third publication reported findings from a large pilot study, which used TREC/KREC levels to screen for inborn errors of immunity.[46] This study included 202,908 infants, who were born in eight regions of Russia, between January 2022 and February 2023. Screening utilised DBS samples and the Eonis™ SCID-SMA kit (Wallac Oy, Turku, Finland), with <100 copies per 10^5 cells being the threshold for an abnormal result for both TREC and KREC. Where the initial TREC and/or KREC levels were below the cut-off, samples were retested (two additional punches from the same Guthrie card). If both repeat test punches were below the TREC and/or KREC cut-off the sample was considered screen positive. For preterm newborns with TREC and/or KREC below the cut-off, a second sample was taken after 4 weeks and, if still screen

positive, subsequently until 42 weeks of postmenstrual age. Infants with a positive screening result were referred for flow cytometry and, where this was abnormal, for genetic diagnosis (whole exome sequencing). Using this algorithm, the retest rate was 5.2%. After all repeat testing, including repeat sampling for preterm newborns, a total of 93 (0.46%) of all newborns remained screen positive. Of the screen positive newborns, 84 received flow cytometry testing (8 refused and 1 died). Eighteen (0.009%) of all newborns screened had abnormal findings on flow cytometry and were referred for genetic testing. The results of genetic testing were reported as 14 cases of inborn errors of immunity (including 7 cases of SCID) one case trisomy and 3 cases of transient idiopathic lymphopenia.[46]

Methodological quality of studies

It is important to note that, although information provided in some reports of experience from implemented screening programmes has been used to calculate measures of screening performance (sensitivity and PPV), these publications do not describe diagnostic test accuracy studies intended to evaluate the diagnostic performance of screening tests or algorithms. Implemented screening does not include the universal application of a diagnostic reference standard; repeat testing and follow-up investigations such as flow cytometry and genetic testing were only carried out where there was an abnormal (screen positive) result. Although reports of implemented screening programmes would not be expected to apply reference standard testing to all samples, it would be theoretically possible to apply a standardised approach to surveillance for missed cases (FN).

QUADAS-2 has been applied to all studies from which measures of screening performance could be derived. We consider the use of QUADAS-2 to be appropriate because the question under consideration (Question 1 — What is the accuracy of the TREC test in population studies of screening for SCID?) is one of test accuracy; it is therefore important to consider the methodological limitations of the included studies in respect of their ability to address this question, irrespective of study design/primary aim.

Table 6 provides a summary of the QUADAS-2 assessments for the seven publications which provided data used to calculate measures of screening performance and the corresponding full QUADAS-2 assessments are provided in Appendix 3.[20, 23-25, 27-29] All of these publications were reports of experience from implemented screening programmes and hence all used a pre-specified TREC cut-off and screening algorithm, and most provided information about the TREC assay used (Table 3). The key methodological issue, given that application of the diagnostic reference standard or long-term follow-up of all screen-negative babies is not practicable, was the lack of a standardised approach to identifying and recording any cases missed by screening. Although three publications stated that no cases of SCID were missed by screening[20, 23, 24] and one publication reported that 2 cases of late-onset SCID were screen-negative,[27] no details were reported regarding how this was determined. The remaining publications did not mention FNs or missed cases at all. It is, therefore, unclear whether the apparently high sensitivity of implemented screening programmes is a reliable representation of the capture of SCID cases.

Table 3: Summary of the TREC-based screening strategies for SCID used in implemented screening programmes

Study	Country (state)	Details of TREC assay	Description of screening algorithm	Description of follow-up/confirmatory testing
Baekvard-Hansen 2021[19]	Denmark	RT-PCR-based TREC quantification using, EONIS™ PCR kit (Perkin Elmer, Turku, Finland). One 3.2 mm DBS punch was used in each sample well.	Initial TREC cut-off <100 copies/10^5 cells, repeat assay in duplicate (same DBS sample) if below cut-off; repeat cut-off <50 copies/10^5 cells, screen positive if below cut-off on repeat. For preterm babies, request new sample at 32 weeks gestation or after 2 weeks if born between 32 and 35 weeks gestation, screen positive if <50 copies/10^5 cells on repeat sample.	Flow cytometry and NGS with an immune-disorder-specific panel.
Booth 2022 [20]	US (Arizona)	NR	Initial TREC cut-off <19 copies/μL, repeat test for term newborns with initial abnormal result, screen positive if <19 copies/μL on repeat. Repeat sampling and assay at term-adjusted gestational age for premature newborns with an initial abnormal result, screen positive if <19 copies/μL on repeat. Urgent referral cut-off <6 copies/μL (evaluated by immunology within 24 hours).	CBC with differential and LSP by flow cytometry in all screen positive newborns, and T-cell phenotyping in newborns with moderate or severe lymphopenia. Second tier testing, in newborns with moderate or severe lymphopenia included T-cell proliferation and genetic testing.

Chan 2021[22]	Singapore	RT-PCR-based TREC quantification using, EONIS™ PCR kit (Perkin Elmer, Turku, Finland). One 1.5 mm DBS punch was used in each sample well.	Initial TREC cut-off <19 copies/μL, repeat assay in duplicate (same DBS sample), repeat with new sample if internal control fails on all samples, screen positive if <19 copies/μL on repeat. Repeat sample every 2 weeks until 32 weeks old in infants <32 weeks, screen positive if <19 copies/μL on repeat. Urgent referral cut-off <4 copies/μL on any test.	Clinical review (history and physical examination) by immunologist, full blood count and immunology testing (lymphocyte subset determination and phenotyping by flow cytometry), followed by genetic evaluation if indicated.
Heather 2022[23]	New Zealand	RT-PCR-based TREC quantification using, EONIS™ PCR kit (Perkin Elmer, Turku, Finland).	Initial TREC cut-off <19 copies/μL, screen positive for term newborns below cut-off. Repeat sample tested at 2 weeks for babies born ≤1,500 g and a further repeat sample tested at 1 month for babies born ≤1,000 g, screen positive if <19 copies/μL on repeat. Urgent referral cut-off <6 copies/μL on any test.	Immunological evaluation, including flow cytometry; no further details reported.
Lev 2022[24]	Israel	RT-PCR-based TREC quantification using, EnLite™ Neonatal TREC kit (Perkin Elmer, UK). One 1.5 mm DBS punch was used in each sample well.	Initial TREC cut-off <17 copies/blood spot, repeat analysis (same DBS sample) in duplicate if below cut-off, request a second sample and repeat process if both repeat analyses <17 copies/blood spot, screen positive if both analyses from the	Immunological evaluations (TREC measurement in peripheral blood, proliferation response to mitogen stimuli, flow cytometry) and whole exome Sanger sequencing.

			second sample are <23 copies/blood spot (cut-off was initially set at 36 copies/blood spot, lowered to 25 copies/blood spot in year 3 and to the current thresholds in year 5)	
Liao 2019[25]	Taiwan	RT-PCR-based TREC quantification, in-house method. One 3.2 mm DBS punch was used in each sample well.	Initial TREC cut-off <50 copies/µL, repeat analysis (same DBS sample) in duplicate if below cut-off, request new DBS sample if consistently <50 copies/µL on repeat, screen positive if repeat samples are consistently <30 copies/µL. For premature newborns repeat DBS at 37 weeks, screen positive if repeat samples are consistently <30 copies/µL.	CBC and flow cytometry
Puck 2021[27]	U.S. (California)	RT-PCR-based TREC quantification using, EnLite™ Neonatal TREC kit (Perkin Elmer, UK).	Initial TREC cut-off <19 copies/µL, repeat analysis (same DBS sample) with actin control if below cut-off, screen positive for newborns in standard care if <19 copies/µL on repeat. For newborns in NICU, <19 copies/µL on repeat analysis, request new heel prick sample and repeat, screen positive if <19 copies/µL. Urgent referral cut-off <4 copies/µL on any test.	CBC with differential and LSP by flow cytometry, referral to specialist immunodeficiency centre where appropriate.

Speckmann 2023[28]	Germany	RT-PCR-based TREC quantification using En-Lite™ commercial kit (Perkin Elmer, Finland), SPOT-it™ commercial kit (ImmunoIVD, Sweden) or an in-house platform.	Initial TREC value below local cut-off (NR), request a new sample and repeat analysis, screen positive if TREC consistently below cut-off. Urgent referral for absent TREC.	Immunological and genetic evaluation at a specialist CID clinic.
Wakamatsu 2022[29]	Japan	RT-PCR-based TREC quantification using En-Lite™ TREC kit, April 2017 to March 2020, TREC/KREC kit, April 2020 to December 2021 (Perkin Elmer, Finland). One 1.5 mm DBS punch was used in each sample well.	Initial TREC cut-off <31 (KREC <21) copies/μL, request new DBS sample and repeat if TREC and/or KREC below cut-off, or refer urgently (no new sample) if TREC <11 copies/μL, screen positive if TREC consistently <31 copies/μL and/or KREC consistently <21 copies/μL.	Immunological evaluation, physical examination, flow cytometry and NGS, within 1 month after birth.

CBC: complete blood count; CID: combined immunodeficiency; DBS: dried blood spot; KREC: kappa-deleting excision circle; LSP: lymphocyte subset panel; NGS: next generation sequencing; NICU: neonatal intensive care unit; NR: not reported; RT-PCR: real time-polymerase chain reaction; SCID: severe combined immunodeficiency; TREC: T-cell receptor excision circle; UK: United Kingdom; US: United States

Table 4: Summary of screening performance based on reported experience following implementation of TREC-based screening for SCID

Study	Study period	Newborns screened, n	Repeat test, n (%)	New sample test, n (%)	SCID, n	Incidence of screen-detected SCID	Non-SCID TCL, n	Incidence of screen-detected non-SCID TCL	PPV, % (95% CI)
Baekvad-Hansen 2021[19]	Feb 2020 to Nov 2020 (yr 1)	53,221	NR (0.25)	NR (NR)	0	N/A	1	1 in 53,221[b] (1.88/100,000)[b]	N/A
Booth 2022[20]	Jan 2018 to Dec 2019 (yr 2-3)	159,730	NR	NR	7	1 in 22,819[a] (4.38/100,000)[b]	15	1 in 10,649 [b] (9.39/100,000)[b]	SCID: 25.93 (18.42, 35.17)[b] TCL: 81.5[a] TCL: 81.48 (64.48, 91.36)[b]
Chan 2021[22]	Oct 2019 to Oct 2020 (yr 1)	35,888	NR (0.1)	23 (0.06)	0	N/A	13[c]	1 in 2,761[b] 36.23/100,000)[b]	N/A
Heather 2022[23]	Dec 2017 to Nov 2020 (yr 1-3)	191,075	NR	NR	2	1 in 95,538[b] (1.05/100,000)[b]	21	1 in 9,099[b] 10.99/100,000)[b]	SCID: 3.85 (2.94, 5.01)[b] TCL: 44.23 (35.53, 53.30)[b]
Lev 2022[24]	Oct 2015 to Sept 2020 (yr 1-5)	937,953	9,784 (1.04)	1,169 (0.12)	30	1 in 31,265[b] (3.20/100,000)[b]	75	1 in 12,506[b] 8/100,000)[b]	SCID: 21.13 (18.21, 24.38)[b] TCL: 73.94 (67.28, 79.66)[b]
Liao 2019[25]	Feb 2012 to Jan 2015 (yr 1-3)	253,999	NR	1,697 (0.67)	2	1 in 127,000[b] (0.79/100,000)[b]	6[d]	1 in 42,333[b] (2.36/100,000)[b]	SCID: 3.57 (2.76, 4.61)[b] 22q11.2 DS: 10.71 (5.90, 18.68)[b]
Puck 2021[27]	Aug 2010 to Mar 2017 (yr 1-7)	3,252,156	NR	NR	50	1 in 65,043[b] 1.54/100,000)[b]	162[c]	1 in 20,075[b] (4.98/100,000)[b]	SCID: 8.90 (8.10, 9.76)[b] TCL: 38[a] TCL: 37.72 (35.29, 40.21)[b]
Speckmann 2023[28]	Aug 2019 to Dec 2021 (yr 1-3)	1,878,985	N/A	1,182 (0.06)	35	1 in 53,685[b] (1.86/100,000)[b]	49[e]	1 in 38,347[b] (2.61/100,000)[b]	SCID: 19.33 (16.93, 21.99)[b] TCL[e]: 26.51 (22.82, 30.56)[b]

									TCL: 34.64 (29.40, 40.29)[b]
Wakamatsu 2022[29]	Apr 2017 to Dec 2021 (yr 1-5)	137,484	N/A	1,147 (0.83)	2	1 in 68,742[b] (1.45/100,000)[b]	58[c]	1 in 2370[b] (42.19/100,000)[b]	SCID: 1.54 (1.30, 1.82)[b] TCL: 60.00 (53.34, 66.31)[b]

[a] Reported
[b] Calculated
[c] Includes transient TCL
[d] 22q11.2 DS was the only non-SCID TCL reported (an additional 7 cases of 22q11.2 DS had TREC values ≥30 and <90 copies µL, i.e. would be missed by the implemented cut-off for SCID screening)
[e] Excluding secondary causes (e.g. prematurity, gastrointestinal lymphangiectasis)
CI: confidence interval; DS: deletion syndrome; N/A: not applicable; NR: not reported; PPV: positive predictive value; SCID: severe combined immunodeficiency; TCL: T-cell lymphopenia; TREC: T-cell receptor excision circle; yr: year

Table 5: Reported screening outcomes following implementation of TREC-based screening for SCID

Study	SCID phenotype	SCID genotype	Syndromic non-SCID TCL	Non-syndromic non-SCID TCL
Baekvad-Hansen 2021[19]	N/A	N/A	Unspecified, n=1	0[a]
Booth 2022[20]	NR	**Total, n=7** Artemis *DLREC1*, n=4 *ADA*, n=1 *IL7R*, n=1 x-linked, n=1	**Total, n=6** 22q11.2 DS, n=2 Soto syndrome, n=1 Dandy-Walker syndrome, n=1 Congenital heart disease, n=1 Trisomy 21, n=1	**Total, n=9**[b] Idiopathic TCL, n=7 Undetermined cause, n=2
Chan 2021[22]	N/A	N/A	**Total, n=3** Trisomy 21 (very premature, died at 2-months), n=1 Trisomy 21 (transient TCL), n=1 Partial 22q11.2 DS (transient TCL), n=1	**Total, n=10** Very premature (died at 5-months), n=1 Transient TCL of prematurity, n=1[c] Sepsis-related, n=2 Transient idiopathic, n=5 Persistent idiopathic, n=1
Heather 2022[23]	NR	NR	**Total, n=11** Complete 22q11.2 DS, n=1 Partial 22q11.2 DS, n=7 CHARGE-associated congenital athymia, n=1 Other (unspecified), n=2	**Total, n=10** TCL of prematurity, n=2 Transient TCL (unspecified), n=7 Idiopathic, n=1
Lev 2022[24]	**Total, n=30** Typical SCID, n=16 Leaky SCID, n=13 Omenn syndrome, n=1	**Total, n=30** *DCLRE1C*, n=11 *IL7R*, n=8 *RAG1*, n=3 *RAG2*, n=1 *IL2RG*, n=1 *JAK3*, n=1 *Ligase4*, n=1 *RFX5*, n=1 *PSMB10*, n=1 *CORO1A*, n=1 *RMRP*, n=1	**Total, n=31** Complete 22q11.2 DS, n=2 Partial 22q11.2 DS, n=10 Trisomy 21, n=6 Cardiac, n=7 Other (unspecified), n=6	**Total, n=44** TCL of prematurity, n=16 Idiopathic, n=16 Sepsis, n=4 Chylothorax, n=5 Other secondary cause (unspecified), n=3
Liao 2019[25]	NR	NR	**Total, n=6**	NR

			22q11.2 DS, n=6[d]	
Puck 2021[27]	**Total, n=50** Typical SCID, n=39 Leaky SCID/Omenn syndrome, n=11	**Total, n=50** *IL2RG*, n=14 *ADA*, n=9 *RAG1*, n=8 *IL7R*, n=6 *JAK3*, n=3 *RAG2*, n=3 *RMRP*, n=1 *BCL11B*, n=1	**Total, n=71** 22q11.2 DS, n=46 Trisomy 21, n=8 Ataxia telangiectasia, n=5 Other (unspecified), n=12	**Total, n=91** Idiopathic TCL, n=33 Transient TCL of prematurity, n=33[e] Hydrops, n=10 Congenital heart disease, n=6 Other congenital abnormalities (unspecified), n=9
Speckmann 2023[28]	**Total, n=35** Typical SCID, n=25 Leaky SCID, n=7 Omenn syndrome, n=3	**Total, n=35** *IL2RG*, n=6 *JAK3*, n=5 *RAG1*, n=4 *DCLRE1C*, n=4 *ADA*, n=4 *FOXN1*, n=3 *IL7RA*, n=2 *RAG2*, n=1 *PNP*, n=1 *BCL11B*, n=1 *NHEJ1*, n=1 *CORO1A*, n=1 *IL1RB*, n=1 Unknown, n=1	**Total, n=42** 22q11.2 DS, n=17 *CHD7*, n=4 *RMRP*, n=3 Trisomy 21, n=3 *FOXI3*, n=1 2p11.2 (*FOXI3*), n=1 *NRAS*, n=1 *PTPN11*, n=1 *EXTL3*, n=1 Ataxia telangiectasia, n=1 *PAX1*, n=1 *PPA2*, n=1 *TP63*, n=1 *RECQL4*, n=1 *HOXA3*, n=1 *SGPL1*, n=1 *TBX1*, n=1 Unknown, n=2	**Total, n=38** Idiopathic TCL, n=4 Reversible TCL, n=2 Undetermined cause, n=1 Secondary cause (e.g. prematurity, gastrointestinal lymphangiectasis), n=31
Wakamatsu 2022[29]	NR	**Total, n=2** *IL2RG*, n=1 Reticular dysgenesis, n=1	**Total, n=35** 22q11.2 DS, n=5 10q11.2-q11.23 microdeletion, n=1 Invdupdel(8p) syndrome, n=1 Cartilage-hair hypoplasia, n=2 CHARGE syndrome, n=2 Wiskott-Aldrich syndrome, n=1 Jacobsen syndrome, n=1	**Total, n=41** TCL of prematurity, n=7 Idiopathic TCL, n=11 Diaphragmatic hernia, n=8 Cardiac anomalies, n=8 Chylothorax, n=4 Congenital CMV infection, n=1 Hydrops, n=1

	Heterozygous *FOXN1*, n=1 Trisomy 21, n=14 Trisomy 18, n=2 Asplenia syndrome, n=2 VACTERL association, n=1 Trisomy 13, n=1 Trisomy 9, n=1	Multiple congenital anomalies, n=1

[a] One preterm (28 weeks) newborn with an initial positive sample was negative on a repeat sample taken 4 weeks after birth.
[b] There were 75 preterm newborns with initially abnormal TREC, which normalised on repeat sample testing at term-adjusted gestational age (screen negative).
[c] A further 7 preterm babies had initially abnormal TREC values which normalised on repeat sampling.
[d] 22q11.2 DS was the only non-SCID TCL reported (the publication aimed to use experience from NBS screening for SCID to evaluate the occurrence of 22q11.2 DS in newborns with different TREC results and to establish a second-tier genetic test for 22q11.2 DS).
[e] T-cell counts rose to normal levels in all preterm infants as they approached full term.
ADA: adenosine deaminase; *BCL11B*: B-cell lymphoma/leukaemia 11B; CHARGE: coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities; *CHD7*: chromodomain helicase DNA binding protein 7; CMV: Cytomegalovirus; *CORO1A*: coronin 1A; *DCLRE1C*: DNA cross-link repair 1C; DS: deletion syndrome; *EXTL3*: exostosin-like glycosyltransferase 3; *FOXN1*: forkhead box N1; *HOXA3*: homeobox A3; *IL2RG*: interleukin-2 receptor subunit gamma; *IL7R:* interleukin 7 receptor alpha chain; Invdupdel(8p): 8p inverted duplication/deletion; *JAK3*: Janus kinase 3; N/A: not applicable; NBS: newborn blood spot; *NHEJ1*: non-homologous end-joining factor 1; NR: not reported; *NRAS*: neuroblastoma *RAS* viral oncogene homolog; *PAX1*: paired box 1; *PPA2*: inorganic pyrophosphatase 2; *PNP*: purine nucleoside phosphorylase; *PSMB10*: proteasome 20S subunit beta 10; *PTPN11*: protein tyrosine phosphatase non-receptor type 11; *RAG1*: recombination-activating gene 1; *RAG2*: recombination-activating gene 2; *RECQL4*: RecQ like helicase 4; *RFX5*: regulatory factor X5; *RMRP*: RNA component of mitochondrial RNA processing endoribonuclease; SCID: severe combined immunodeficiency; *SGPL1* sphingosine-1-phosphate lyase 1; TBX1: T-box transcription factor 1; TCL: T-cell lymphopenia; *TP63*: tumour protein 63; TREC: T-cell receptor excision circle; VACTERL: vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities

Table 6: Summary of QUADAS-2 evaluations

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Booth 2022[20]	✓	✓	×	×	✓	✓	✓
Heather 2022[23]	✓	✓	×	×	✓	✓	✓
Lev 2022[24]	✓	✓	×	×	✓	✓	✓
Liao 2019[25]	✓	✓	×	×	✓	✓	✓
Puck 2021[27]	✓	✓	×	×	✓	✓	✓
Speckmann 2023[28]	✓	✓	×	×	✓	✓	✓
Wakamatsu 2022[29]	✓	✓	×	×	✓	✓	✓

✓ Low Risk × High Risk ? Unclear Risk

Discussion of findings

Most of the studies included in this evidence summary were retrospective reports of experience from existing screening programmes, some of which provided updated, larger data sets for programmes already included in the 2017 UK NSC evidence review, the most recent review of TREC-based NBS screening for SCID.[4] The 2017 UK NSC evidence review included a report of screening experience in the US that included data from the screening programmes of 10 States plus the Navajo Area Indian Health Service, describing a total of 1,265 referrals from over 3 million newborns screened.[6] The current evidence summary includes a more recent report of screening in the state of California, with over 3 million screened newborns from this state alone,[27] as well as a report of screening in the state of Arizona,[20] where screening was implemented after the date of the previous review. We did not identify any studies which included long-term follow-up of screen-negative babies, or which reported details of any standardised process for identifying and recording any cases of SCID missed by screening.

Four of the reports of screening experience, included in the current evidence summary, either stated that no missed (screen-negative) cases of SCID were identified during the reported period[20, 23, 24] or that all screen-negative cases identified were late onset SCID.[27] These studies provide some support for the conclusion of the previous review that TREC-based screening, as implemented in existing NBS screening programmes, has high sensitivity for the target condition SCID. However, it should be noted that, given the apparent lack of a standardised approach to identifying and recording any cases missed by screening, it remains uncertain whether the apparently high sensitivity of implemented screening programmes is a reliable representation of the capture of SCID cases.

The 2017 UK NSC evidence review included calculated PPVs of screening, including for data from the USA[6] which were taken from a published systematic review.[66] It was noted that these values indicated that TREC-based NBS screening has poor PPV for SCID, with most values falling between 2% and 15% and the lowest value being 0.8% (Texas).[4] For the current evidence summary, we have calculated PPVs for all new data sets identified. Our calculated PPVs were generally higher, with most values falling between 3.6% and 26%; the only value outside this range was 1.6% (Japan). Our calculated values for PPV (8.9%), incidence of SCID/100,000 (1.54) and incidence of TCL/100,000 (4.98), for the updated California data set,[27] were similar to those previously published for California (11.2%, 1.7 and 5.8, respectively).[66] As

noted in the previous review, differences in PPVs may be explained by differences in screening algorithms.[4] Geographical variation in the prevalence of SCID and syndromic non-SCID TCLs may also account for some of the variation in observed PPVs.

The 2017 UK NSC evidence review highlighted the issue of FP screening results in preterm babies. The current evidence summary therefore sought information on the accuracy of TREC-based NBS screening for SCID in relevant subgroups (preterm babies and sick babies). Although we did not identify any subgroup data, the included reports of screening experience appear to indicate a growing use of screening algorithms that incorporate a repeat sampling step for preterm/low birth weight or sick babies with an initially abnormal TREC result. The numbers of reported cases of TCL of prematurity were generally highest in those screening programmes which did not include use of a repeat sample for premature babies;[24, 29] although the report of the California screening programme[27] reported 33 cases of transient TCL of prematurity, this publication also noted that T-cell counts rose to normal levels in all premature infants as they approached full term. The report of the Arizona screening programme also noted that there were 75 preterm births with initially abnormal TREC, which normalised at term.[20] There was, therefore, some evidence to indicate that the use of screening algorithms incorporating repeat sampling (e.g. at term-adjusted gestational age) in preterm babies can markedly reduce FP results due to transient TCL of prematurity.

A study-level summary of accuracy and partial accuracy data extracted from each included publication is presented in 'Summary and appraisal of individual studies Appendix 3'.

Summary of Findings Relevant to Criterion 4

The 2017 UK NSC evidence review[4] concluded that criterion 4, *'There should be a simple, safe, precise and validated screening test,'* was only partially met. This conclusion was based on the poor PPV observed for the TREC assay. The review further noted that, though there was evidence of high sensitivity from existing screening programmes, at the TREC cut-off values used, the test identifies newborns with other non-SCID TCLs and FP results are observed in preterm babies.[4]

Additional data, from existing screening programmes in the US and other countries, included in this evidence summary is consistent with the findings of the previous review; at the cut-off values needed to maintain high sensitivity, the TREC assay has poor PPV for SCID. There is some evidence, particularly from screening programmes in the US, that the use of screening algorithms that include repeat sampling (e.g. at term-adjusted gestational age) in preterm babies can markedly reduce FP results due to transient TCL of prematurity. However, even where FP results due to prematurity are reduced or eliminated, the large number of other conditions that can give rise to a low TREC value (positive screening result) mean that the PPV for SCID remains consistently poor. Whether or not criterion 4 is considered to be met is therefore likely to be substantially dependent upon how non-SCID TCLs (incidental findings) are treated.

Summary of Findings Relevant to Criterion 5

The 2017 UK NSC evidence review[4] noted that the distribution of TREC values in the UK population had been tested[65] and a suitable cut-off for the UK population could be defined. The review, therefore, concluded that criterion 5, *'The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed,'* was met.[4]

This evidence summary did not identify any new UK studies that met the inclusion criteria for question 1. An ISE of newborn screening for SCID has recently completed in English NHS services.[17] The evidence base available for inclusion in this report has, therefore, not changed since the previous review.

Findings from the ISE may provide more up to date information on test and cut-off values from a large UK sample (criterion 5). The ISE also has the potential to provide UK-specific insights into how incidental findings have been handled in practice, including care pathways and outcomes for these children and their families (criterion 4).

Criterion 9 — Efficacy of treatment in the pre-symptomatic phase

Criterion 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.

Evidence to inform criterion 9 was included in the 2017 UK NSC evidence review.[4] The 2017 UK NSC evidence review concluded that criterion 9 was met.

Question 2 — Does HSCT (or gene therapy or thymic transplant, if appropriate) in SCID cases detected during the asymptomatic period lead to improved out-comes?

The 2017 UK NSC evidence review considered the question: 'Does early HSCT lead to improved outcomes compared with late HSCT in SCID patients?'

The 2017 UK NSC evidence review stated that there was evidence to show that HSCT is an effective treatment for SCID and that early transplant has been consistently shown to improve survival outcomes. This statement was supported by data from studies where early diagnosis was made due to family history of SCID, and by studies that statistically analysed the relationship between age at transplant and survival.[4] The 2017 UK NSC evidence review did not include any studies which examined the effect of diagnosing SCID through NBS screening on survival and/or other outcomes following treatment. The 2017 UK NSC evidence review concluded that the evidence supports the statement, *'there is an effective treatment with evidence that early treatment improves prognosis,'* that there is further evidence about the conditions under which HSCT may be more or less effective, and that this criterion was therefore met.[4]

What is added by this evidence review

This evidence review provides an updated summary of the published studies available to inform question 2. Importantly, all of the studies included in this evidence review provide some information about the effect of diagnosing SCID through NBS screening on survival and/or other outcomes following treatment.

The inclusion criteria for this evidence summary (Table 2) specified the consideration of the effects of early identification of SCID (through NBS screening, cascade testing or a combination

of both) on outcomes following treatment, where treatments considered included gene therapy or thymic transplant as well as HSCT.

Description of new evidence in relation to previous evidence reviews

The searching and title and abstract screening stages of the evidence review were conducted as a single process, with consideration of all three research questions. Appendix 2 provides an overall PRISMA flow chart for this evidence summary and details of studies included and excluded after full text screening.

Following full text screening, there were six publications that met the inclusion criteria specified for research question 2.[30-32, 56, 63, 64] Two of these publications[63, 64] were included in both the previous evidence review about the addition of TREC-based screening for SCID to an NBS screening programme (the 2017 UK NSC evidence review[4] and the Republic of Ireland HIQA report[1]); both of these publications provided information about the effects of early diagnosis of SCID due to family history. One further publication[56] was included in the Republic of Ireland HIQA report only;[1] this publication used data from the Primary Immune Deficiency Treatment Consortium (PIDTC), for a subset of the patients included in the more recent (2023) publication, by Thakar et al., described below.[31] Publications previously included in the 2017 UK NSC evidence review or the Republic of Ireland HIQA report are not included in this evidence summary.

All three of the new publications included in this evidence summary some provide information about the effect of diagnosing SCID through NBS screening on survival and/or other outcomes following treatment with HSCT.[30-32] No studies were identified that evaluated the effects of early diagnosis on outcomes following other treatments (gene therapy or thymic transplant). Study details, participant characteristics and details of HSCT are provided in Tables 7 to 9. All three publications reported pairwise comparisons that provided information about the effects of the route of diagnosis (including NBS screening) on survival after HSCT; the results of these analyses are summarised in Table 10. Thaker et al. 2023 and Scheutz et al. 2023 also reported the results of multivariable regression analyses exploring factors effecting survival after HSCT.[31, 32] Thaker et al. 2023 described models that included route of diagnosis as an independent variable.[31] The model reported in Scheutz et al. 2023 was based on a substantially smaller data set and did not include route of diagnosis as an independent variable; however, the effect of age at HSCT on organ damage before HSCT (a strong negative determinant of overall survival [OS]) was explored (Table 14).[32] The results of published multivariable analyses are summarised in Tables 11 to 13. Scheutz et al. 2023 and Soomann et al. 2024 reported additional pairwise comparisons for the effects of route of diagnosis (including NBS screening) on outcomes other than survival (e.g. rates of complications and rates of repeat procedures);[30, 32] the results of these analyses are summarised in Table 15.

Schuetz et al. 2023[32]

Schuetz et al. 2023 used data from a worldwide cohort (n=60) of patients with hypomorphic recombination-activating gene (*RAG*) variants, who received their first transplant between 2004 and 2019, to explore factors affecting outcome following HSCT. The study excluded patients who presented as typical SCID or Omenn phenotype. There were 8/60 (13%) participants who were diagnosed as a result of NBS screening or family history (FH).[32]

Overall, 47/60 (78%) of participants experienced infections before HSCT and 17/58 (29%) had an active infection at the time of transplant, 47/60 (78%) had autoimmunity and/or granuloma pre-transplant, and 34/60 (57%) had organ damage.[32]

Overall survival (OS) was estimated using Kaplan-Meier analyses, censored at the last follow-up before the end of the study (8 February 2021) and log-rank test was used to compare survival curves.[32]

Forty-two patients were alive at last follow-up with most deaths occurring in the first 12-months after HSCT. Overall, estimated OS at 1 and 4 years were 77.5% and 67.5%, respectively. Early diagnosis via NBS screening or FH was reported to be associated with a non-statistically significant survival benefit, compared with clinical diagnosis (p=0.064) and survival of patients diagnosed via NBS screening or FH was 100%. Early HSCT (defined using a cut-off of age <3.5 years at transplant) had no statistically significant effect on OS (Table 10).[32]

Hazard ratios (HRs) for potential risk factors for death were calculated by univariable Cox regression. A multivariable model was constructed using Cox regression with stepwise forward selection; only variables that were significant at the p=0.05 level in the univariable analysis were added successively to the multivariable model and eliminated stepwise. Logistic regression was used to find determinants for significant variables. In the final model, organ damage before HSCT and T-cell depletion remained significant predictors of death with HRs of 6.01 (95% CI: 1.72 to 21) and 8.46 (95% CI: 3.22 to 22.24), respectively (Table 13). '*Owing to the strong negative impact of pre-HSCT organ damage on OS',* the study authors used logistic regression to explore factors that may be associated with its occurrence; autoimmunity and/or granuloma before HSCT, age ≥3.5 years at HSCT, infection before HSCT and delay of >12 months from birth to diagnosis were found to be significant predictors of organ damage before HSCT (Table 14).[32]

With respect to immune reconstitution, Scheutz et al. 2023 reported that $CD4^+CD45RA^+$ T-cell count rose faster in patients who underwent transplant before the age of 3.5 years than in those who underwent later transplant, the probability of naïve $CD4^+$ T-cell count reaching the age-adjusted normal reference range was also higher in the earlier transplant group (60% compared to 20%), (Table 15).[32]

The analyses reported in Schuetz et al. provide some indirect evidence that delayed diagnosis (>12 month) and late (≥3.5 years) HSCT may be associated with poorer survival following HSCT and that these effects are likely to be mediated by the development of complications (e.g. infections and organ damage) during the period of delay. The study also found improved immune reconstitution on patients who received earlier transplant (<3.5 years of age), providing further indirect evidence for a beneficial effect of early diagnosis.

Soomann et al. 2024[30]

Soomann et al. 2024 reported results from a small study which compared the outcomes of SCID patients who were diagnosed through Switzerland's national programme of NBS screening for SCID, introduced in January 2019, (n=7) with those of a historical cohort who were diagnosed with SCID (clinical presentation) between 2007 and 2019, (n=15).[30]

Categorical variables were compared using Fisher's exact test and continuous variables were compared using the Mann-Witney *U*-test. Survival time was defined as the time from first HSCT

to death. OS was estimated using Kaplan-Meier analyses, censored at the last clinical follow-up and log-rank test was used to compare survival curves.[30]

Children diagnosed after the introduction of the NBS screening programme were similar to those in the historical control group, with respect to demographic, disease and transplant characteristics (Tables 8 and 9).[30]

Children diagnosed via NBS screening were significantly younger at diagnosis than those in the historical cohort, median age 9 days (range: 4 to 13 days), than those in the historical cohort, median age 9 months (range 3 days to 13 years). Children in the NBS screening group also underwent earlier HSCT, median age at transplant 5 months (range 4 to 8 months), than those in the historical cohort, median age at transplant 11 months (range 3 months to 17 years). The rate of pre-HSCT infections was lower in the NBS screening group, 2/7 (29%), than in the clinical diagnosis groups, 14/15 (93%) and although the difference was not statistically significant, the rate of OS at last follow-up was higher in the NBS screening group (86%) than in the clinical group (67%), p=0.62. Survival analysis also indicated a non-statistically significant higher OS probability in the NBS screening group, 0.41 (95% CI: 0.05 to 3.55), (Table 10).[30]

Soomann et al. 2024 also compared rates of HSCT complications and secondary procedures, discontinuation of immunoglobulin replacement, and myeloid chimerism, in the NBS screening and clinical diagnosis groups; no significant between-group differences were observed for these outcomes, (Table 15).[30]

This study provides some indication that earlier diagnosis and treatment with HSCT, following the introduction of a national NBS screening programme, may have been associated with improvements in survival for SCID patients. However, the data set was very small and observed differences in survival did not reach statistical significance.

Thakar et al. 2023[31]

Thakar et al. 2023 reported results from a series of analyses of transplant-related data from the US PIDTC, collected over four decades from 34 sites in the US; the final dataset included 902 children with SCID. These analyses explored demographic, disease-related and transplant-related variables affecting the survival of individuals with SCID and focused on the effects of the NBS screening programme for SCID (initiated in 2008 and expanded over the subsequent 10 years).[31]

Changes in survival over time were considered using calendar intervals 1982 to 1989, 1990 to 1999, 2000 to 2009 and 2010 to 2018. The χ^2 test was used to compare categorical variables and the Kruskal-Wallis test was used for continuous variables. OS was estimated using Kaplan-Meier analyses, censored at the last clinical follow-up. Univariate comparisons of OS were performed using the log-rank test. Risk factors for transplant outcomes (survival) were assessed using multivariable Cox proportional hazards regression models, with bi-directional stepwise selection and a p value ≤0.05 indicative of statistical significance.

Five-year survival was unchanged (72% to 73%) for the first 28 years of the data set (1982 to 2009). In the NBS screening period (2010 to 2018) 5-year survival increased to 87% (95% CI: 82.1% to 90.6%) and subgroup analyses showed that 5-year survival during this period was higher for children identified via NBS screening, 92.5% (95% CI: 85.8% to 96.1%), than for those identified by FH, 85.4% (95% CI: 71.8% to 92.8%), or clinical illness, 79.9% (95% CI: 69.5% to 87.0%), (Table 10). Univariate analysis of OS by time interval showed that survival

improved in the 2010 to 2018 period, compared to earlier periods, HR 0.46 (95% CI: 0.29 to 0.75).[31]

To explore which factors contributed to the observed improvement in survival, since 2010, demographic, clinical and transplant-related variables were collected and compared for each time period; a summary of this data, for the pre-NBS screening (1982 to 2009) and NBS screening (2010 to 2018) is provided in Tables 8 and 9. Multivariable analysis including variables found to be significant on univariable analysis found that, after adjusting for active infection at transplant, age ≥3.5 years at transplant, genotypes with inferior survival (*ADA*, DNA repair defects, rarely identified and unknown genes compared with the most common genotype *IL2RG/JAK3*), and Black or African American race, the time period in which transplant occurred was no longer a significant predictor of OS, (Table 11). The multivariable analysis excluded transplant using human leukocyte antigen (HLA)-matched sibling donors, since this factor was consistently associated with high rates of survival (≥92%) across all time periods.[31]

A second multivariable Cox regression analysis was conducted to examine the effect of route of diagnosis on OS. This model adjusted for the same variables included in the first model, with the exception of age at transplant and infection history at transplant; these two variables were omitted because they are potential drivers of the effects of early diagnosis (i.e. NBS screening can lead to earlier transplant and reduced infection exposure, and hence to improved OS). This analysis found that, compared with clinical illness, diagnosis via NBS screening or FH were both associated with improved survival, HR 0.32 (95% CI: 0.15 to 0.67) and HR 0.52 (95% CI: 0.37 to 0.74) for the event of death, respectively, (Table 12). In order to establish that the effect of route of diagnosis on OS was not attributable to the confounding effects of time period, this second multivariable analysis was repeated for the screening period (2010 to 2018) subgroup; the subgroup analysis confirmed that, compared with clinical illness, diagnosis via NBS screening was associated with improved survival, HR 2.96 (95% CI: 1.32 to 6.65), and was similar to that for diagnosis via FH, HR 1.70 (95% CI: 0.59 to 4.86), (Table 12). Sensitivity analysis, on the screening period (2010-2018) subgroup, using propensity scoring, further confirmed that diagnosis via NBS screening was associated with improved OS compared with clinical diagnosis, HR 2.55 (95% CI: 1.12 to 5.80).[31]

Thakar et al. 2023 also examined changes in the incidence of graft versus host disease (GvHD) over time and found that, whilst the incidence of chronic GvHD remained unchanged, there was a decline in the incidence of grade 3-4 acute GvHD after 2010 (during the NBS screening period). At day-180 post-transplant the cumulative incidence of grade 3-4 GvHD was 0.105 (95% CI: 0.057 to 0.170), 0.140 (95% CI: 0.098 to 0.189), 0.088 (95% CI: 0.059 to 0.125), and 0.061 (95% CI: 0.037 to 0.095), for the time periods 1982 to 1989, 1990 to 1999, 2000 to 2009, and 2010 to 2018, respectively.[31]

This study provides robust evidence that early diagnosis is associated with improved post-transplant survival for patients with SCID and that this effect is likely to be driven by earlier and transplant and reduced infection burden.

Methodological quality of studies

All three of the publications included in this evidence summary reported retrospective studies.[30-32] Both Schuetz et al. 2023[32] and Thakar et al. 2023[31] reported the results of multivariable regression analyses, which were undertaken with the aim of identifying factors predictive of post-treatment (HSCT) survival in patients with SCID. The methodological quality of these two studies was therefore assessed using the QUIPS tool, which was developed to assess risk of

bias in studies of prognostic factors.[43] Table 16 provides a summary of these assessments and the corresponding full QUIPS assessments are provided in Appendix 3. The study attrition domain has been rated as 'not applicable' for both studies, because factors relating to loss to follow-up are not relevant to retrospective analyses of records-derived data. Both Schuetz et al. 2023[32] and Thakar et al. 2023[31] were rated as low risk of bias on all of the remaining 5 domains of the QUIPS tool (study participation, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting). It is, however, important to note that the analyses reported in Thakar et al. 2023 are more comprehensive and are likely to be more robust than those reported in Schuetz et al. 2023; because of the much larger sample size (n=902 patients with SCID compared to 60 patients with SCID in Schuetz et al. 2023), as well as the long period for which data was available (28 years), Thakar et al. 2023 were able to more fully explore the predictors of OS (including early diagnosis), as well as potential confounders and factors which may be driving any observed effects.

Soomann et al. 2024 reported a very small retrospective study, comparing the outcomes of patients with SCID after the introduction of the national NBS screening programme in Switzerland to those of a historical cohort of patients diagnosed with SCID in the 12 years immediately prior to the introduction of the screening programme. The methodological quality of this study has been assessed using the modified version of the CASP checklist for cohort studies of treatment, as used in the 2017 UK NSC evidence review;[4] the results of this assessment are provided in Appendix 3. Although the findings of Soomann et al. 2024[30] are broadly consistent with those of Thakar et al. 2023[31] and Scheutz et al. 2023,[32] effect estimates are less precise due to the very small sample size and are reliant upon less robust methods of analysis (pairwise comparisons, which do not account for potential confounding).

Discussion of findings

All three of the new publications included in this evidence summary provide information about the effects early diagnosis on the post-transplant outcomes of patients with SCID who are treated with HSCT.[30-32] These publications add to the 2017 UK NSC evidence review,[4] in that they all provide information on the effects of route of diagnosis, and NBS screening in particular, on post-transplant outcomes; the evidence base at the time of the previous review meant that the authors relied upon indirect evidence, from studies where early diagnosis was made due to FH and studies that analysed the relationship between age at transplant and survival, to infer conclusions about the probable effects of NBS screening on treatment outcomes.

Schuetz et al. 2023 considered the effects of age at transplant (using a cut-off point of <3.5 years) on post-transplant outcomes and also provided a direct comparison of survival curves for patients who were diagnosed via NBS screening or FH versus patients diagnosed via other routes.[32] Soomann et al. 2024[30] directly compared post-transplant outcomes in patients diagnosed with SCID after the introduction of the national NBS screening programme for SCID in Switzerland with those of a historical control group who were diagnosed with SCID due to clinical illness, before the introduction of screening. Thakar et al. 2023 provided the key evidence in relation to question 2 (criterion 9); data from the US PIDTC, collected over a 28 year period provided a large sample (n=902) of patients with SCID, which supported a comprehensive exploration of factors affecting the survival of patients with SCID after HSCT and the extent to which observed improvements in survival could reliably be attributed to the introduction of NBS screening.[31]

Scheutz et al. 2023[32] and Soomann et al. 2024[30] both reported that early diagnosis of SCID, via NBS screening or FH and following the introduction of NBS screening, respectively, was

associated with non-statistically significant improvements in post-transplant survival. Thakar et. al. 2023 reported the results of multivariable Cox regression analyses, adjusted for demographic disease-related and transplant-related variables found to be significant on univariate analysis, which showed that diagnosis of SCID via NBS screening significantly improved OS compared to diagnosis via. clinical presentation; this effect remained consistent when the analysis was repeated in the screening period (2010 to 2018) subgroup, to account for the potential confounding effects of time period, and in a sensitivity analysis using propensity scoring.[31] Overall, the findings of these studies, in particular those of Thakar et al. 2023[31] support the conclusion that early diagnosis of SCID through NBS screening is associated with improvements in survival after treatment with HSCT.

Evidence about the effects of early diagnosis of SCID on other outcomes post-HSCT was very limited. Soomann et al. 2024 reported complications, secondary procedures, discontinuation of immunoglobulin replacement and myeloid chimerism, but found no significant differences between patients diagnosed with SCID before and after the introduction of NBS screening, for any of these outcomes.[30] Schuetz et al. 2023 reported significantly better immune reconstitution in patients with SCID who received HSCT before the age of 3.5 years, providing indirect evidence of a potential benefit of early diagnosis. Finally, Thakar et al. 2023 reported that the incidence of grade 3-4 GvHD, which was unchanged over the time periods from 1982 to 2009, declined in the period after the introduction of NBS screening (2010 to 2018), however, no analyses to explore potential confounding effects were reported for this outcome.[31]

Of further note, no studies were identified that evaluated the effects of early diagnosis on outcomes following treatments than HSCT (e.g. gene therapy or thymic transplant).

Summary of Findings Relevant to Criterion 9

The 2017 UK NSC evidence review[4] concluded that the criterion, *'there should be an effective treatment with evidence that early treatment improves prognosis,'* was met. The 2017 UK NSC evidence review stated that there was evidence to show that HSCT is an effective treatment for patients with SCID and that early transplant has been consistently shown to improve survival outcomes. This statement was supported by data from studies where early diagnosis was made due to FH of SCID, and by studies that statistically analysed the relationship between age at transplant and survival.[4] The 2017 UK NSC evidence review did not include any studies which directly assessed the effect of diagnosing SCID through NBS screening on survival and/or other outcomes following treatment.

All three of the new publications included in this evidence summary provide information about the effect of diagnosing SCID through NBS screening on survival and/or other outcomes following treatment with HSCT.[30-32] The findings of all three studies support the conclusion that diagnosis of SCID through NBS screening is associated with improvements in survival after treatment with HSCT. Although the effect sizes reported by Schuetz et al. 2023[32] and Soomann et al. 2024[30] did not reach statistical significance, the direction of effect remained consistent. The large sample size and series of well-designed and clearly reported analyses presented in Thakar et al. 2023 provide robust evidence that early diagnosis through NBS screening is associated with improved post-transplant survival for SCID patients and that this effect is likely to be driven by earlier and transplant and reduced infection burden. The analyses presented in Thaker et al. 2023 included an analysis restricted to the screening period (2010-2018) subgroup, to account for the potential confounding effects of time period (i.e. potential effects of improvements in HSCT over time. We therefore consider that criterion 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,' is met for screening-detected SCID. However, for many non-SCID conditions, treatment options remain limited and long-term prognosis unclear. Evaluating the harms and benefits resulting from screen detection of non-SCID conditions is a methodological challenge both for the non-SCID cases themselves and for gauging the balance of benefits and harms of NBS for SCID.

Table 7: Details of studies assessing the effects of early diagnosis on outcomes following HSCT

Study	Country	Study design	Participants	Timeframe	Outcomes assessed
Schuetz, 2023[32]	Global (PIDTC and (ESID)	Retrospective analysis of European registry (EMBT) data and data from PIDCT (NCT01346150) Univariable and multivariable Cox regression analyses; diagnosis by 'newborn or family screening' was not included in any multivariable analyses.	60 patients treated at 31 centres (40 patients in Europe, 18 in North America and 2 in Australia). Patients were eligible for inclusion if they had a confirmed RAG1/RAG2 deficiency, had >300 autologous T-cells at diagnosis or had <300 T-cells but had received no HSCT before the age of 18 months. Patients with RAG1/RAG2 deficiency presenting as typical SCID or Omenn syndrome were excluded.	2004 to 2019	OS Immune reconstitution ($CD4^+$ T-cell reconstitution and $CD4^+CD45RA^+$ T-cell reconstitution)
Soomann, 2024[30]	Switzerland	Retrospective analysis comparing outcomes of SCID patients identified through Switzerland's NBS screening programme with those of a historical cohort.	22 Patients fulfilling the ESID criteria for SCID or atypical SCID.	NBS screening cohort (2019 to 2021) Historical cohort (2007 to 2019)	OS Complications (including) GvHD Myeloid chimerism at last follow-up Discontinuation of immunoglobulin replacement Secondary procedures
Thakar, 2023[31]	US and Canada (PIDTC)	Retrospective study, analysing HSCT-related data from a 36-year longitudinal	902 children with SCID, treated (HSCT) at 34 PIDTC sites.	1 January 1982 to 31 December 2018 (2010-2018 for the	5-year survival rate OS Acute GvHD Chronic GvHD

	study, using time intervals 1982 to 1989, 1990 to 1999, 2000 to 2009, and 2010 to 2018. A multivariable analysis using Cox proportional hazards regression models; trigger for diagnosis of SCID (FH, newborn screening, clinical illness, unknown) was included as a categorical variable.	Patients were enrolled in two PIDTC natural history studies (NCT01346150 and NCT01186913). Eligible patients had either typical SCID or atypical SCID (including leaky SCID, Omenn syndrome or reticular dysgenesis).	'newborn screening era' subgroup)

EMBT: European Society for Blood and Marrow Transplantation; ESID: European Society for Immunodeficiencies; FH: family history; GvHD: graft versus host disease; HSCT: hematopoietic stem cell transplantation; OS: overall survival; PIDTC: Primary Immune Deficiency Treatment Consortium; RAG1/RAG2: recombination-activating gene 1/2; SCID: severe combined immunodeficiency; US: United States

Table 8: Participant characteristics for studies assessing the effects of early diagnosis on outcomes following HSCT

Study	Group (N)	Sex, n (%)	Age at diagnosis, median (range)	Diagnostic route, n (%)	SCID type, n (%)	SCID genotype, n (%)	Clinical symptoms before HSCT, n (%)
Schuetz, 2023[32]	All (60)	M, 27 (45) F, 33 (55)	3.3 (0, 39.9), y	NBS screening or FH, 8 (13) Other 52 (87)	Atypical SCID, 60 (100)	*RAG1*, 46 (77) *RAG2*, 14 (23) Homozygous, 19 (32) Compound heterozygous, 41 (68)	Infection, 47 (78) Active infection, 17/58 (29) Autoimmunity/granuloma, 47 (78) Organ damage, 34 (57)
Soomann, 2024[30]	All (22)	M, 16 (73) F, 6 (27)	5 m (3 d, 13 y)	NBS screening, 7 (32)	T-B-NK-, 1 (4) T-B-NK+, 9 (41)	*RAG1*, 5 (23) *RAG2*, 1 (4.5)	Infection, 16 (73) Active infection, 7 (32)

				Clinical, 15 (68)	T-B+NK-, 5 (23) T-B+NK+, 7 (32)	*ADA*, 2 (9) *LIG4*, 1 (4.5) *NHEJ1*, 1 (4.5) *IL2RG*, 6 (27) *IL7R*, 3 (14) *RMRP*, 2 (9) *JAK3*, 1 (4.5)	Autoimmunity, 6 (27) Organ damage, NR
	NBS screening (7)	M, 7 (100) F, 0 (0)	9 (4, 13), d	-	T-B-NK-, 1 (14) T-B-NK+, 3 (43) T-B+NK-, 1 (14) T-B+NK+, 2 (29)	*RAG1*, 3 (44) *RAG2*, 0 *ADA*, 1 (14) *LIG4*, 0 *NHEJ*, 0 *IL2RG*, 1 (14) *IL7R*, 0 *RMRP*, 1 (14) *JAK3*, 1 (14)	Infection, 2 (29) Active infection, 1 (14) Autoimmunity, 0 Organ damage, NR
	Clinical (15)	M, 9 (60) F, 6 (40)	9 m (3 d, 13 y)	-	T-B-NK-, 0 T-B-NK+, 6 (40) T-B+NK-, 4 (27) T-B+NK+, 5 (33)	*RAG1*, 2 (13.5) *RAG2*, 1 (6.5) *ADA*, 1 (6.5) *LIG4*, 1 (6.5) *NHEJ1*, 1 (6.5) *IL2RG*, 5 (33.5) *IL7R*, 3 (20) *RMRP*, 1 (6.5) *JAK3*, 0	Infection, 14 (93) Active infection, 6 (40) Autoimmunity, 6 (40) Organ damage, NR
Thakar, 2023[31]	1982 to 2009 (pre-NBS screening period) (634)	M, 457 (72) F, 177 (28)	NR	NBS screening, 0 FH, 208 (33) Clinical, 416 (66) Unknown, 10 (1)	Typical, 566 (89) Atypical, 68 (11) Leaky, 39 (6) Omenn syn-drome, 25 (4) Reticular dys-genesis, 4 (0.6)	*ADA*, 44 (7) *DCLRE1C/LIG 4/NHEJ1*, 27 (4) *IL2RG/JAK3*, 208 (33) *IL7R, CD3* (any), *CD45,* 46 (7) *RAG1/RAG2*, 43 (7)	Infection, 468 (74) Active infection, 297 (47) Autoimmunity, NR Organ damage, NR

					Other identified, 2 (0.3) Unknown, 264 (42)	
2010 to 2018 (NBS screening period) (268)	M, 166 (62) F, 102 (38)	NR	NBS screening, 130 (49) FH, 49 (18) Clinical, 89 (33) Unknown, 0	Typical, 181 (68) Atypical, 87 (33) Leaky, 65 (75) Omenn syndrome, 17 (20) Reticular dysgenesis, 5 (6)	*ADA*, 11 (4) *DCLRE1C/LIG4/NHEJ1*, 14 (5) *IL2RG/JAK3*, 91 (34) *IL7R, CD3* (any), *CD45*, 28 (10) *RAG1/RAG2*, 63 (23) Other identified, 27 (10) Unknown, 34 (13)	Infection, 134 (50) Active infection, 82 (31) Autoimmunity, NR Organ damage, NR
2010 to 2018 NBS screening (130)	NR	NR	-	NR	NR	Infection, 44 (34) Active infection, 27 (21) Autoimmunity, NR Organ damage, NR
2010 to 2018 Family history (49)	NR	NR	-	NR	NR	Infection, 17 (35) Active infection, 6 (12) Autoimmunity, NR Organ damage, NR
2010 to 2018 Clinical (89)	NR	NR	-	NR	NR	Infection, 73 (82) Active infection, 24 (27) Autoimmunity, NR Organ damage, NR

ADA: adenosine deaminase; d: days; *DCLRE1C*: DNA cross-link repair 1C; F: female; FH: family history; HSCT: hematopoietic stem cell transplant; *IL2RG*: interleukin 2 receptor gamma; *IL7R*: interleukin 7 receptor alpha chain; *JAK3*: Janus kinase 3; *LIG4*: DNA ligase 4; m: months; M: male; n: number; NBS: newborn blood spot; *NHEJ1*: non-homologous end-joining factor; NR: not reported; *RAG1*: recombination activating gene 1; *RAG2*:

recombination activating gene 2; *RMRP*: RNA component of mitochondrial RNA-processing endoribonuclease; SCID: severe combined immunodeficiency; y: years

Table 9: Details of HSCT for studies assessing the effects of early diagnosis on outcomes following HSCT

Study	Group (n)	Age at HSCT, median (range), n (%)	Donor, n (%)	Graft, n (%)	Conditioning, n (%)	GvHD prophylaxis, n (%)
Schuetz, 2023[32]	All (60)	3.4 (0.23, 42.9), y <3.5 y, 31 (52) ≥3.5 y, 29 (48)	MRD, 13 (22) MMRD, 11 (18) MUD, 29 (48) MMUD, 7 (12)	Bone marrow, 35 (58) Cord blood, 7 (12) PBSC, 18 (30)	MAC, 19 (32) RIC/RTC, 40 (67) Other/none, NR	ATG, 32 (53) Alemtuzumab, 17 (28)
Soomann, 2024[30]	All (22)	10 m (3 m, 17 y)	MRD, 3 (14) MMRD, 3 (14) MUD, 11 (50) MMUD, 5 (22)	NR	MAC, 2 (9) RIC/RTC, 17 (77) Other/none, 3 (14)	CsA, 5 (23) CsA + MMF, 16 (73) CsA + MMF + sirolimus, 1 (4)
	NBS screening (7)	5 (4, 8), m	MRD, 0 MMRD, 1 (14) MUD, 6 (86) MMUD, 0	NR	MAC, 0 RIC/RTC, 7 (100) Other/none, 0	CsA, 0 CsA + MMF, 6 (86) CsA + MMF + sirolimus, 1 (14)
	Clinical (15)	11 m (3 m, 17 y)	MRD, 3 (20) MMRD, 2 (14) MUD, 5 (33) MMUD, 5 (33)	NR	MAC, 2 (13) RIC/RTC, 10 (67) Other/none, 3 (20)	CsA, 5 (33) CsA + MMF, 10 (67) CsA + MMF + sirolimus, 0
Thakar, 2023[31]	1982 to 2009 (pre-NBS screening period) (634)	<3.5 y, 166 (26) ≥3.5 y, 468 (74)	MRD, 113 (18) MMRD, 409 (65) MUD, 21 (3) MMUD, 21 (3) Cord blood, 64 (10) Unknown, 6 (1)	Bone marrow, 477 (75) Cord blood, 64 (10) PBSC, 93 (15)	MAC, 139 (22) RIC/RTC, 57 (9) Immunosuppression, 101 (16) Conditioned (unknown), 5 (<1) None, 332 (52)	T-cell depletion, 337 (53) CD34 selection+/- T-cell depletion, 84 (13) Pharmacological immunosuppression, 63 (10) Pharmacological immunosuppression + ATG or alemtuzumab, 113 (18) None, 37 (6)
	2010 to 2018 (NBS screening period) (268)	<3.5 y, 126 (47) ≥3.5 y, 142 (53)	MRD, 47 (18) MMRD, 63 (24) MUD, 68 (25) MMUD, 18 (7)	Bone marrow, 146 (55) Cord blood, 71 (27) PBSC, 51 (19)	MAC, 75 (28) RIC/RTC, 98 (37) Immunosuppression, 32 (12)	T-cell depletion, 16 (6) CD34 selection+/- T-cell depletion, 61 (23)

		Cord blood, 71 (27) Unknown, 1 (<1)		Conditioned (unknown), 1 (<1) None, 62 (23)	Pharmacological immunosuppression, 51 (19) Pharmacological immunosuppression + ATG or alemtuzumab, 129 (48) None, 11 (4)
2010 to 2018 NBS screening (130)	92.5 (IQR: 67, 114), d <3.5 y, 87 (67) ≥3.5 y, 43 (33)	NR	NR	NR	NR
2010 to 2018 Family history (49)	76 (IQR: 49, 132), d <3.5 y, 31 (63) ≥3.5 y, 18 (37)	NR	NR	NR	NR
2010 to 2018 Clinical (89)	252 (IQR: 152,461), d <3.5 y, 8 (9) ≥3.5 y, 81 (91)	NR	NR	NR	NR

ATG: antithymocyte globulin; CsA: ciclosporin A; d: days; GvHD: graft versus host disease; HSCT: hematopoietic stem cell transplant; IQR: interquartile range; m: months; MAC: myeloablative conditioning; MMF: mycophenolate mofetil; MMRD: mismatched related donor; MMUD: mismatched unrelated donor; MRD: matched related donor; MUD: matched unrelated donor; n: number; NBS: newborn blood spot; NR: not reported; PBSC: peripheral blood stem cells; RIC: reduced intensity conditioning; RTC: reduced toxicity conditioning; y: years

Table 10: Pairwise comparisons of survival following HSCT, by route of diagnosis

Study	Group (N)	Number with outcome n/N or survival median (range)	Follow-up, median (range)	Effect size (95% CI)
		Overall survival		
Schuetz, 2023[32]	NBS screening or FH (8) Clinical (52) Age <3.5 y at HSCT (31) Age ≥3.5 y at HSCT (29)	NR NR NR NR	All, 39 (NR, NR) m, Survivors, 57 (NR, NR) m	p = 0.064 p = 0.6
Soomann, 2024[30]	NBS screening (7) Clinical (15)	NR NR	Survivors, NR (23m, 15 y)	HR, 0.41 (0.05, 3.55) p = 0.42
		5-y survival		
Thakar, 2023[31]	2010 to 2018 NBS screening (130) 2010 to 2018	92.5% (95% CI: 85.8%, 96.1%) 85.4% (95% CI: 71.8%, 92.8%)	- -	NBS screening versus FH, p = 0.184

	FH (49) 2010 to 2018 Clinical (89)	79.9% (95% CI: 69.5%, 87%)	-	NBS screening versus Clinical, p = 0.012 FH versus Clinical, p = 0.491

CI: confidence interval; FH: family history; HR: hazard ratio; HSCT: hematopoietic stem cell transplant; m: months; n: number with outcome; N: number in group; NBS: newborn bloodspot; NR: not reported; y: years

Table 11: Multivariable analysis of factors with a significant negative effect on OS following HSCT[31]

Independent variable	Number with event[a] (n)	HR[b] (95% CI)	*P* value	Overall *p* value
All (1982 to 2018)				
Infection at time of transplant				
No infection	241	1.00	-	<0.0001
Actively infected	324	2.41 (1.56, 3.72)	<0.0001	
Resolved infection	189	1.24 (0.76, 2.03)	0.382	
Unknown	20	1.81 (0.78, 4.23)	0.169	
Age at transplant				
<3.5 months	238	1.00	-	0.0005
≥3.5 months	536	2.12 (1.38, 3.24)	0.0005	
Genotype				
IL2RG/JAK3	274	1.00	-	<0.0001
ADA	46	2.22 (1.23, 4.01)	0.008	
DCLRE1C/LIG4/NHEJ1	31	3.67 (1.83, 7.35)	0.0002	
IL7R, CD3 (any), *CD45*	66	1.26 (0.68, 2.34)	0.464	
RAG1, RAG2	83	1.72 (0.96, 3.09)	0.069	
Other identifies genotypes	25	3.32 (1.48, 7.45)	0.004	
Unknown/NR	249	2.50 (1.77, 3.54)	<0.0001	
Race				
White	545	1.00	-	0.0002
Native American/Native Alaskan	31	0.92 (0.45, 1.85)	0.810	
Asian/Pacific Islander	31	1.84 (0.98, 3.44)	0.058	
Black or African American	72	2.33 (1.56, 3.46)	<0.0001	
Unknown/Not declared	95	1.56 (1.05, 2.30)	0.026	
Time interval of transplant				
1982 to 1989	102	1.00	-	0.097
1990 to 1999	192	1.20 (0.79, 1.81)	0.388	

2000 to 2009	255	1.26 (0.83, 1.91)	0.276
2010 to 2018	225	0.73 (0.43, 1.26)	0.261

Note: This analysis also included the following non-significant variables: Type of SCID (atypical versus typical); route of diagnosis (NBS screening, FH, or clinical); ethnicity; donor type; stem cell source; conditioning regimen; GvHD prophylaxis; use of T-cell depletion. The analysis did not include transplantation from HLA matched siblings as this was associated with consistently higher OS at all time intervals; the study authors noted that including the HLA-matched sibling group would have inhibited the ability of the model to detect differences between route of diagnosis in the non-sibling donor groups.

[a] Event defined by death

[b] HR for the event of death

ADA: adenosine deaminase; CD3: cluster of differentiation 3; CD45: cluster of differentiation 45; CI: confidence interval; *DCLRE1C*: DNA cross-link repair 1C; FH: family history; GvHD: graft versus host disease; HLA: human leukocyte antigen; HR: hazard ratio; HSCT: hematopoietic stem cell transplant; *IL2RG*: interleukin 2 receptor gamma; *IL7R*: interleukin 7 receptor alpha chain; *JAK3*: Janus kinase 3; *LIG4*: DNA ligase 4; NBS: newborn blood spot; *NHEJ1*: nonhomologous end-joining factor; NR: not reported; OS: overall survival; *RAG1*: recombination-activation gene 1; *RAG2:* recombination-activation gene 2; SCID: severe combined immunodeficiency

Table 12: Multivariable analysis of factors with a significant negative effect on OS following HSCT, removing age at HSCT and infection status at HSCT and adding route of diagnosis[31]

Independent variable	Number with event[a] (n)	HR[b] (95% CI)	*P* value	Overall *p* value
All (1982 to 2018)				
Route of diagnosis[c]				
Clinical	434	1.00	-	
FH	215	0.52 (0.37, 0.74)	<0.001	<0.001
NBS screening	115	0.32 (0.15, 0.67)	0.003	
Genotype				
IL2RG/JAK3	270	1.00	-	
ADA	46	1.89 (1.05, 3.40)	0.034	
DCLRE1C/LIG4/NHEJ1	30	3.57 (1.74, 7.35)	0.001	
IL7R, CD3 (any), *CD45*	66	1.22 (0.65, 2.26)	0.537	<0.001
RAG1, RAG2	82	1.54 (0.85, 2.79)	0.155	
Other identifies genotypes	25	2.92 (1.31, 6.54)	0.009	
Unknown/NR	245	2.29 (1.61, 3.25)	<0.001	
Race				
White	538	1.00	-	
Native American/Native Alaskan	29	0.97 (0.47, 2.04)	0.946	<0.001
Asian/Pacific Islander	31	2.11 (1.12, 3.95)	0.020	

Black or African American	72	2.22 (1.49, 3.30)	<0.001	
Unknown/Not declared	94	1.76 (1.19, 2.60)	0.005	
Time interval of transplant				
1982 to 1989	100	1.00	-	
1990 to 1999	185	1.12 (0.74, 1.70)	0.601	0.508
2000 to 2009	254	1.13 (0.74, 1.73)	0.557	
2010 to 2018	225	0.79 (0.44, 1.42)	0.430	
Subgroup analysis, for event defined as survival, 2010 to 1028 (NBS screening period)[d]				
Route of diagnosis				
Clinical	115	1.00	-	
FH	40	1.70 (0.59, 4.86)	0.322	0.031
NBS screening	70	2.96 (1.32, 6.65)	0.008	

Note: This analysis also included the following non-significant variables: Type of SCID (atypical versus typical); ethnicity; donor type; stem cell source; conditioning regimen; GvHD prophylaxis; use of T-cell depletion. The analysis did not include transplantation from HLA matched siblings as this was associated with consistently higher OS at all time intervals; the study authors noted that including the HLA-matched sibling group would have inhibited the ability of the model to detect differences between route of diagnosis in the non-sibling donor groups.

[a] Event defined by death

[b] HR for the event of death

[c] Patients with an unknown route of diagnosis were excluded

[d] The subgroup analysis adjusted for genotype and race, as in the overall model

ADA: adenosine deaminase; CD3: cluster of differentiation 3; CD45: cluster of differentiation 45; CI: confidence interval; *DCLRE1C*: DNA cross-link repair 1C; FH: family history; GvHD: graft versus host disease; HLA: human leukocyte antigen; HR: hazard ratio; HSCT: hematopoietic stem cell transplant; *IL2RG*: interleukin 2 receptor gamma; *IL7R*: interleukin 7 receptor alpha chain; *JAK3*: Janus kinase 3; *LIG4*: DNA ligase 4; NBS: newborn blood spot; *NHEJ1*: nonhomologous end-joining factor; NR: not reported; OS: overall survival; *RAG1*: recombination-activation gene 1; *RAG2:* recombination-activation gene 2; SCID: severe combined immunodeficiency

Table 13: Multivariable analysis of factors with a significant negative effect on OS following HSCT[32]

Independent variable	Number with event[a] (n)	Univariable model		Stepwise multivariable model	
		HR[b] (95% CI)	*P* value	HR[b] (95% CI)	*P* value
Infection before HSCT	47	5.71 (0.76, 43.01)	0.091	-	-
Active infection at HSCT	17	4.57 (1.77, 11.79)	0.002	-	-
Organ damage	34	4.58 (1.32, 15.83)	0.016	6.01 (1.72, 21.00)	0.005
MMRD	11	4.97 (1.91, 12.90)	0.001	-	-

T-cell depletion	15	6.79 (2.61, 17.664)	<0.001	8.46 (3.22, 22.24)	<0.001

Note: non-significant variables in the univariable analyses were: autoimmunity before HSCT; year of HSCT; age at HSCT; graft (bone marrow, cord blood or PBSC); type of conditioning regimen
[a] Event defined by death
[b] HR for the event of death
CI: confidence interval; HR: hazard ratio; HSCT: hematopoietic stem cell transplant; MMRD: mismatched related donor

Table 14: Exploration of factors effecting organ damage before HSCT[32]

Variable	**Organ damage before HSCT, n (%)**			
	No	**Yes**	**OR (95% CI)**	***P* value**
Autoimmunity and/or granuloma before HSCT				
No	11 (42.3)	2 (5.9)	-	-
Yes	15 (57.7)	32 (94.1)	11.73 (2.73, 82.27)	0.003
>12 months from birth to diagnosis				
No	7 (30.4)	2 (6.2)	-	-
Yes	16 (69.6)	30 (93.8)	6.56 (1.40, 47.67)	0.029
Infection before HSCT				
No	10 (38.5)	3 (8.8)	-	-
Yes	16 (61.5)	31 (91.2)	6.46 (1.70, 31.95)	0.010
Age at HSCT ≥3.5 y				
No	19 (73.1)	12 (35.3)	-	-
Yes	7 (26.9)	22 (64.7)	4.98 (1.69, 16.04)	0.005

CI: confidence interval; HSCT: hematopoietic stem cell transplant; n: number with event; OR: odds ratio; y: years

Table 15: Pairwise comparisons of other HSCT outcomes, by route of diagnosis

Study	**Group (N)**	**Number with outcome n or median (range)**	**Follow-up, median (range)**	**Effect size (95% CI)**
		$CD4^+$ T-cell reconstitution		
Schuetz, 2023[32]	Age <3.5 y at HSCT (31)	NR	NR	*p* = 0.081
	Age ≥3.5 y at HSCT (29)	NR	NR	
		$CD4^+CD45RA^+$ T-cell reconstitution		
Schuetz, 2023[32]	Age <3.5 y at HSCT (31)	NR	NR	*p* = 0.017

	Age ≥3.5 y at HSCT (29)	NR	NR	
		CD3+ T-cell count		
Schuetz, 2023[32]	Age <3.5 y at HSCT (31)	NR	NR	p = 0.01
	Age ≥3.5 y at HSCT (29)	NR	NR	
		CD8+ T-cell count		
Schuetz, 2023[32]	Age <3.5 y at HSCT (31)	NR	NR	p = 0.03
	Age ≥3.5 y at HSCT (29)	NR	NR	
		CD4+ T-cell count		
Schuetz, 2023[32]	Age <3.5 y at HSCT (31)	NR	NR	p = 0.081
	Age ≥3.5 y at HSCT (29)	NR	NR	
		Discontinuation of immunoglobulin replacement		
Soomann, 2024[30]	NBS screening (7)	83%	NR	'no significant difference'
	Clinical (15)	80%	NR	
		Complications		
Soomann, 2024[30]	NBS screening (7)	Graft failure, 0 VOD, 0 Acute GvHD, 2 Chronic GvHD, 1	NR	Graft failure, p = 0.26 VOD, p = 0.26 Acute GvHD, p = 0.65 Chronic GvHD, p > 0.99
	Clinical (15)	Graft failure, 4 VOD, 4 Acute GvHD, 7 Chronic GvHD, 2	NR	
		Myeloid chimerism at last follow-up		
Soomann, 2024[30]	NBS screening (7)	<2%, 0 2-10%, 1 10-90%, 3 ≥90%, 3 Unknown, 0	NR	p = 0.82
	Clinical (15)	<2%, 2 2-10%, 2 10-90%, 2 ≥90%, 8 Unknown, 1	NR	
		Secondary procedures		
Soomann, 2024[30]	NBS screening (7)	Stem cell boost, 0 Second HSCT, 0	NR	p = 0.67

		None, 7	
	Clinical (15)	Stem cell boost, 1 Second HSCT, 3 None, 11	NR

CI: confidence interval; GvHD: graft versus host disease; HSCT: hematopoietic stem cell transplant; n: number with outcome; N: number in group; NBS: newborn blood spot; NR: not reported; VOD: veno-occlusive disease; y = year

Table 16: Summary of QUIPS assessments

Study	Risk of bias Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Schuetz, 2023[32]	✓	NA	✓	✓	✓	✓
Thakar, 2023[31]	✓	NA	✓	✓	✓	✓

✓ Low Risk × High Risk NA not applicable

QUIPS: Quality in Prognosis Studies

Criterion 6 — Acceptability of NBS for SCID

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

Evidence to inform criterion 6 was not considered in the 2017 UK NSC evidence review[4] conducted for the UK NSC. The Republic of Ireland HIQA report[1] included a chapter on the ethical and social considerations associated with the addition of screening for SCID of the NBS screening programme, but did not undertake a systematic review of the evidence about the acceptability of NBS screening for SCID.

Question 3 — Is the experience of population screening for SCID acceptable to parents and carers of newborn babies?

This question was not considered by the 2017 UK NSC evidence review.[4] A separate, unpublished, systematic review (Chambers et al. 2023) has subsequently been undertaken, which aimed to identify and synthesise available research on the acceptability to parents/carers of NBS screening and newborn genomic/exomic sequencing.[10] Although this review included one study about the acceptability of NBS screening for SCID,[11] the overall aim was to consider the acceptability of NBS screening in general rather than acceptability in relation to screening for any one condition. Adequate consideration of criterion 6, through consideration of acceptability evidence that is specific to NBS screening for SCID, is important because broader evidence about the acceptability on NBS screening programmes may not be generalisable to the acceptability of screening for specific conditions. This is particularly important given that NBS screening for SCID is associated with high rates of incidental findings and the potential to identify conditions for which there may be no effective treatment. In addition, the Chambers et al. 2023 review was limited to studies conducted in parents of newborns (first month of life) who were eligible for or who took part in blood spot screening or genomic/exomic sequencing and studies of future parents during their pregnancy (i.e. antenatal phase); any evidence about the attitudes to screening of parents who had experienced more complex diagnostic pathways following a positive screening result (particularly relevant to incidental findings in NBS for SCID) would, therefore, be unlikely to be captured by this review.[10]

What is added by this evidence review

This evidence review provides a summary of the published studies available to inform question 3. Importantly, this evidence review focuses on studies which address the acceptability of NBS for SCID to parents and carers. In addition, this review did not limit the inclusion of studies on the basis of time elapsed since experience of screening. This evidence review, therefore, has the potential to capture evidence about parental attitudes to screening at the end of the diagnostic pathway, and/or following a non-SCID positive screening result.

The inclusion criteria for this evidence summary (Table 2) specified the consideration measures of parental acceptability/perceptions of screening, including psychosocial measures (e.g. anxiety, depression, coping strategies) and knowledge related measures (e.g. understanding of the screening process and the condition being screened for).

Description of new evidence in relation to previous evidence reviews

The searching and title and abstract screening stages of the evidence review were conducted as a single process, with consideration of all three research questions. Appendix 2 provides an overall PRISMA flow chart for this evidence summary and details of studies included and excluded after full text screening.

Following full text screening, there were six publications that met the inclusion criteria specified for research question 3.[11, 33-37] All six publications are described in this section including one publication[11] which was included in the Chambers et al. 2023 review,[10] from which additional data has been extracted.

The six included publications explored parental and carer attitudes to the acceptability of SCID screening in newborns from a variety of perspectives. Three publications reported studies conducted in the context of the pre-implementation pilot of the Netherlands national NBS screening for SCID programme; 1 study explored the perspectives of parents (including both parents of healthy newborns and parents of newborns with a positive SCID screening result) on the implementation of NBS screening for SCID,[11] 1 study focused on issues around the reporting of incidental findings from NBS screening for SCID considering the perspectives of parents of healthy newborns on this issue and using the example of a finding of A-T,[33] and 1 study considered the perspectives of multiple stakeholders (including parents of children with unspecified abnormal and normal NBS screening results) on the expansion of the Netherlands NBS screening programme (including the addition of NBS screening for SCID).[34] The challenge of untreatable unsolicited findings was discussed using the example of NBS screening for SCID.[34] Two publications reported studies that explored uncertainties and coping strategies experienced by the parents of children diagnosed with SCID through NBS screening programmes in the US[35, 37] The final publication reported findings from a Patient and Public Involvement and Engagement (PPIE) activity that sought to identify the information needs of families of infants with suspected athymia following NBS screening for SCID; families had been referred to the thymus transplantation program at GOSH, London, UK, following NBS screening (26 centres across 19 countries).[36]

The studies employed various methodologies, including interviews, surveys, and focus groups, to capture qualitative[11, 33-37] and quantitative[11, 33] data on themes related to emotional impact, communication, uncertainty, and decision-making following abnormal results on NBS screening for SCID. The studies involved sample sizes ranging from 9 to 664 participants, with diverse parental demographics and healthcare settings. An overview of these studies is provided in Table 17. Qualitative study findings were extracted and synthesised with consideration to the core domains of acceptability described in the Chambers et al. 2023 report (Figure 1).[10] Table 18 provides a summary of findings across the core themes.

Choice and consent

Across the studies, choice and consent were recurring themes, particularly in discussions surrounding the ethical complexities of expanding NBS screening to include conditions like SCID and the potential for incidental detection of untreatable disorders.

In Blom et al. 2021, parents expressed concerns about the lack of informed choice prior to screening.[11] Many felt that the implications of screening for SCID were not fully explained, and they desired more comprehensive consent procedures. This was especially important for parents confronted with incidental findings that fell outside SCID diagnoses. The study

recommended that NBS screening programmes provide parents with clearer information pre-screening, enabling more informed choices.[11] Similarly, van Dijk et al. 2021 emphasised the need for personalised consent, where parents could opt to exclude untreatable or late-onset conditions from the screening.[34] The study suggested consent procedures that allow for parental autonomy, balancing health gain with ethical considerations.[34]

Blom et al. 2019 explored parental attitudes towards the reporting of incidental findings from NBS screening for SCID, using the example of a finding of A-T.[33] Parents overwhelmingly supported screening, but they also expressed mixed emotions about how much choice they should have in including such conditions in NBS screening. Some favoured early diagnosis, while others preferred to avoid the knowledge of untreatable conditions during a child's early, asymptomatic years.[33] Of note, all participants in Blom et al. 2019 were parents of healthy newborns and the study did not, therefore capture the perspectives of parents who had experienced receiving an incidental finding.[33]

Information provision

A consistent finding across the studies was that information provision, following a positive NBS screening result, was often perceived as inadequate or delayed, leaving parents feeling confused and anxious. Blom et al. 2021 highlighted how, following a positive NBS screening result, parents reported receiving insufficient and sometimes incorrect information from general practitioners (GPs) who lacked specialist knowledge about SCID. This led to significant distress, especially when abnormal results were delivered without sufficient explanation. Parents indicated that clear, detailed information before and after screening was crucial in reducing their anxiety.[11]

Howley et al. 2024 echoed these concerns, reporting that many parents of children suspected of having SCID or congenital athymia felt they received fragmented and delayed information. In some cases, parents were informed about SCID but not about the possibility of athymia until much later in the diagnostic process. The lack of consistent information flow contributed to heightened confusion and distress, pushing parents to seek information from online sources. The study recommended that healthcare providers offer comprehensive, accessible information early in the diagnostic process to reduce uncertainty.[36]

In Raspa et al. 2024, parents also expressed the need for ongoing information provision throughout the SCID journey, as the condition's complexity often led to evolving uncertainties. Parents wanted regular updates from healthcare providers, tailored to the different stages of their child's treatment and post-treatment.[35]

Weighing up risks and benefits

Blom et al. 2019 asked the parents of healthy newborns to consider advantages and disadvantages for both early and late diagnosis of A-T. Around a quarter of participants stated that they could see no advantages for late diagnosis; the main advantage cited was enjoyment of the asymptomatic years without worry/anxiety. The main disadvantages given for late detection concerned the hereditary nature of the condition and not being able to make fully informed decisions about family planning and pre-natal diagnosis. Parents also associated late diagnosis with delayed medical access (guidance and surveillance of the patient and family), a long period of uncertainty and worries, and delayed breast cancer screening for the mother of the patient. Some parents also mentioned not being able to prepare, mentally and financially for a diagnosis. The main advantage of early diagnosis, from the parents' perspective, was the

ability to start supportive treatment and receipt of optimal clinical guidance from the outset; specialist surveillance was also mentioned. Parents highly valued clarity and knowing what to expect in contrast to uncertainty and insecurity associated with a late diagnosis. Other advantages mentioned were early breast cancer screening for the mother of the patient and ability to make informed reproductive choices. Disadvantages of early diagnosis were mainly linked to difficulty in processing such devastating news in the emotional period after birth and feelings of insecurity about the future.[33] It is important to note that this study was conducted in parents of healthy newborns and, as such, the reported perceptions may not be representative of those of parents who experience an incidental finding as a result of NBS screening for SCID.

Parental perspectives on the advantages and disadvantages of early diagnosis, in the context of NBS screening, are summarised in Table 19.

The procedure

There were no included studies that reported acceptability outcomes relating to the screening procedure.

Notification of results

The process of notifying parents about screening results was a pivotal source of emotional strain reported across the studies. Information about the emotional impact of the notification of results is summarised in Table 20. Information about the support needs of parents and reported recommendations for improving communication are summarised in Table 21.

Blom et al. 2021 found that the majority of parents were notified of abnormal results via telephone, often by non-specialist GPs who were unable to provide in-depth explanations. This method of communication was viewed as impersonal and rushed, intensifying parents' anxiety. The study suggested that tandem calls involving both primary healthcare providers and specialists could improve the notification process, allowing for more detailed explanations and reducing parental distress.[11]

Howley et al. 2024 reported that delayed or incomplete notifications regarding SCID or athymia diagnoses contributed to parental confusion. Parents reported that clinicians often delivered results in a piecemeal fashion, without a full explanation of the differential diagnoses and potential treatment options. This delay caused undue stress, and the study recommended earlier and clearer communication of potential diagnoses to prepare parents emotionally and practically.[36]

The timing and clarity of result notifications were also found to be important, with parents expressing that the uncertainty surrounding SCID diagnoses was exacerbated by unclear notifications. This led to emotional distress that could have been mitigated by more comprehensive and compassionate communication from healthcare providers.[35, 37]

van Dijk et al. 2021 reported that many parents indicated that they would want to be informed about any disorder detected through NBS screening, irrespective of treatability. Parents thought that an incidental finding involving an early diagnosis of an untreatable condition could be beneficial in saving medical visits and tests in search of a diagnosis and may reduce the period of uncertainty following the onset of symptoms in their child. In addition, some parents stated that they preferred to learn about a diagnosis of an untreatable condition at an early stage, giving them time to prepare and anticipate symptoms in their child. One parent expected that

some parents might want to know about untreatable disorders because it may influence their decision about a future pregnancy.[34]

Trust in the healthcare system

Following an abnormal SCID NBS screening result, all parents reported experiencing significant anxiety and emotional insecurity up to the hospital visit, however, this did not change their trust in the NBS screening programme.[11] Parental trust in the healthcare system, and specifically in the newborn screening process, was shaped by the quality of communication and the perceived competence of healthcare providers. Blom et al. 2021 found that parents generally had greater trust in paediatric immunologists than in GPs, particularly when it came to delivering and explaining SCID screening results. When referred to specialists, parents felt reassured and more confident in the accuracy of the diagnosis and the appropriateness of the treatment plan.[11] This trust, however, was eroded when results were delivered by less knowledgeable healthcare professionals, highlighting the importance of specialist involvement in the screening process.

Howley et al. 2024 found that parental trust in the healthcare system was undermined when there were delays in providing information or when the diagnostic process appeared fragmented. However, trust was restored when parents had access to clinical nurse specialists (CNS) or paediatric immunologists who could offer detailed, consistent support throughout the screening and diagnostic journey.[36]

Kutsa et al. 2022 underscored the importance of trust in medical teams as a key coping mechanism for parents navigating the SCID journey. Parents who felt they could rely on their healthcare providers for guidance and clear communication experienced lower levels of anxiety. The study emphasised the need for healthcare providers to maintain open and trustworthy relationships with families to support them during this emotionally challenging time.[37]

Additional themes — Uncertainties and coping strategies

Two studies explored the uncertainties experienced by parents of children diagnosed with SCID through NBS screening programmes in the US,[35] and with their coping strategies across the stages of their SCID journey (diagnosis, pre-treatment, treatment, post-treatment and new normal).[37] Parents experienced a variety of chronic uncertainties across all stages, with some being more prevalent at certain stages and others spanning the whole journey. Uncertainties were coded into 4 main types (scientific, practical, personal and existential); scientific uncertainty dominated in the early (diagnosis and pre-treatment) stages, with sources of uncertainty becoming more evenly distributed in the later (new normal) stage.[37] Levels of all types of uncertainty were lowest during the treatment phase.[37] Parents expressed a variety of negative emotional responses to uncertainty, including anxiety, worry, fear, doubt, guilt or grief, anger, frustration and depression.[37] Coping strategies were categorised as behavioural, cognitive or emotional. Behavioural strategies included active information seeking (e.g. researching SCID, consulting specialists and connecting with other SCID families) and active participation in treatment decisions (e.g. questioning doctors, seeking second opinions and managing care). Cognitive strategies included focusing on what can be controlled (following expert medical advice and identifying actionable steps) and positive reframing (using positive thinking and focusing of their child's progress). Emotional strategies included trusting medical professionals for emotional support and reassurance, leaning on peer support from other SCID families or spiritual/religious practices for comfort.[35, 37]

Quantitative results

Blom et al. 2021 included findings from interviews with parents of 17/23 newborns referred with an abnormal SCID result. The majority (15/17) were very satisfied with the rapid availability of diagnostic results and the provision of follow-up by a paediatric immunologist. However, with respect to the issue of informed consent prior to participation, only 8/17 parents remembered receiving information about NBS screening for SCID prior to the heel prick and knowingly participated in the pilot; one mother questioned whether she would have participated if she had been formally asked. Parental perception of the vulnerability of their newborn was assessed using the vulnerable baby score (VBS), n=13; the mean (standard deviation [SD]) VBS was 28.8 (4.8) compared with 23.1 (3.1) in healthy control newborns.[11]

Blom et al. 2021[11] and Blom et al. 2019[33] included quantitative information (responses to closed statements on a 5-point Likert scale, where 1 = completely disagree and 5 = completely agree) about the attitudes of parents of healthy newborns to NBS screening for SCID; these response data is provided in Table 22. The majority of respondents expressed support for NBS screening for SCID from both a public health perspective, *"I think it is important that SCID is included in the newborn screening programme,"* (mean rating 4.3) and a personal perspective, *"SCID is a severe disorder and I want this disorder to be detected as early as possible for my child,"* (mean rating 4.2).[11]

Of the 664 parents of healthy newborns who participated in Blom et al. 2019, 81.9% favoured early diagnosis of A-T over late and the most (81.1%) also stated that they would participate in NBS screening for A-T if a test were available.[33] The reasons underpinning parental views on early versus late diagnosis were explored using responses to closed statements on a 5-point Likert scale, where 1 = completely disagree and 5 = completely agree; these response data is provided in Table 22. The main reasons for favouring early diagnosis were avoidance of a long period of uncertainty before diagnosis and ensuring optimal care and guidance from the occurrence of first symptoms.[33]

Methodological quality of studies

The methodological quality of all six included studies was assessed using the MMAT.[44] With the exception of Howley et al. 2024,[36] all studies received a positive rating on the majority of relevant questions and can be regarded as being of good methodological quality. Limited reporting of methods meant that Howley et al. 2024 was rated 'cannot tell (CT)' on the majority of relevant questions; however, it is important to note that Howley et al. 2024 is a report of findings from a PPIE activity and not a formal qualitative research study, and as such the methodological quality assessment is of questionable value. Full results of the MMAT assessment are provided in Appendix 3.

In addition to the MMAT assessments, a summary of the reported validation procedures, used in qualitative studies, is provided in Table 23.

Discussion of findings

Overall, qualitative data from the publications included in this evidence summary was indicative of parental support for NBS screening for SCID. Two large studies, conducted in connection with the pre-implementation pilot of NBS for SCID in the Netherlands, found support amongst parents of healthy newborns for NBS screening for SCID, from both public health and personal perspectives,[11] as well as support for screening for untreatable conditions/reporting of incidental findings (A-T).[33] These two studies represent the largest available data sets on the acceptability, to parents, of NBS screening for SCID. Blom et al. 2021[11] was the only study to assess the

views of the whole screening-eligible population (parents of healthy newborns as well as parents of newborns with a positive screening result). Of note, although all parents of newborns with a positive screening result reported experiencing significant anxiety and emotional insecurity prior to the hospital follow-up visit, they did not feel that this affected their trust in the NBS screening programme, and most (15/17) were very satisfied with the follow-up process.[11]

The Netherlands study of stakeholder perspectives on the expansion of the NBS screening programme noted that many stakeholders (including parents) emphasised treatability and health gain as a prerequisite for inclusion of a disorder in the programme.[34] With respect to incidental findings, this study reported that many parents indicated that they would want to be informed about any disorder detected through NBS screening, irrespective of the availability of treatments. In addition to their appreciation for receiving detailed medical information, parents expressed the view that early diagnosis of an untreatable condition could be beneficial, as it would save medical visit and tests in search of a diagnosis and reduce the period of uncertainty following the first appearance of symptoms. Parents also stated that they preferred to learn about an untreatable condition at an early stage to give them time to prepare.[34]

None of the smaller studies, conducted in parents of newborns with a positive result on NBS screening for SCID, explicitly reported information about parental support for screening,[35-37] although all families of children with suspected athymia, who participated in the PPIE activity reported by Howley et al. 2024 acknowledged the importance of NBS screening in keeping their children safe: *"If (our child) hadn't had that NBS, (they) probably would not be here now"*; *"(Our child) is still infection-free and I think it wouldn't be possible if we were not isolated."*[36]

The emotional strain experienced by parents following abnormal NBS SCID screening results was a consistent theme across all studies. Negative experiences and unmet needs appeared to be concentrated around the notification of (abnormal) screening results and timely access to specialist information and support.[11, 36, 37 35]

There was also some evidence of problems with ensuring informed consent, with approximately half of the parents of newborns with an abnormal screening result who participated in Blom et al. 2021 stating that they did not remember receiving information and agreeing to participate in the pilot of NBS screening for SCID.[11]

Summary of findings relevant to criterion 6

Evidence to inform criterion 6 was not considered in the 2017 UK NSC evidence review.[4]

A separate, unpublished, systematic review (Chambers et al. 2023) has subsequently been undertaken, which aimed to identify and synthesise available research on the acceptability to parents/carers of NBS screening and newborn genomic/exomic sequencing.[10] However, the overall aim of this study was to consider issue of acceptability of NBS screening in general rather than acceptability of NBS screening for SCID and it was therefore not adequate to address criterion 6.

This evidence summary found some evidence of parental support for NBS screening for SCID, primarily from studies connected to the pre-implementation pilot conducted in the Netherlands, as well as some evidence that parents regarded the early identification of non-SCID conditions (incidental findings) as advantageous irrespective of treatability and that there was support for reporting of such findings.[11, 33, 34] However, the majority of evidence came from parents of healthy newborns and there remains a paucity of evidence derived from parents who have

experienced a positive result on NBS screening for SCID and in particular those who have experienced a positive screening result and a subsequent non-SCID diagnosis (incidental finding).

There was also evidence of unmet needs around informed consent and provision of information and support following a positive NBS screening result.[11, 36, 37 35] In addition, none of the evidence in this section is derived from studies of the screening experience in the UK; in the PPIE study involving families of infants referred to the thymus transplantation program at GOSH, London, UK, infants had been identified by NBS screening programmes across 19 countries.[36] This lack of UK data may create some uncertainty about the generalisability of the review findings to the UK setting and further complicates the picture.

We therefore consider that, whilst there is some evidence of parental support for NBS screening for SCID and for the early identification of non-SCID conditions (incidental findings), further work (e.g. stakeholder dialogue Patient and Public Involvement activities) may be helpful to establish whether criterion 6, *'the test, from sample collection to delivery of results, should be acceptable to the target population,'* is met.

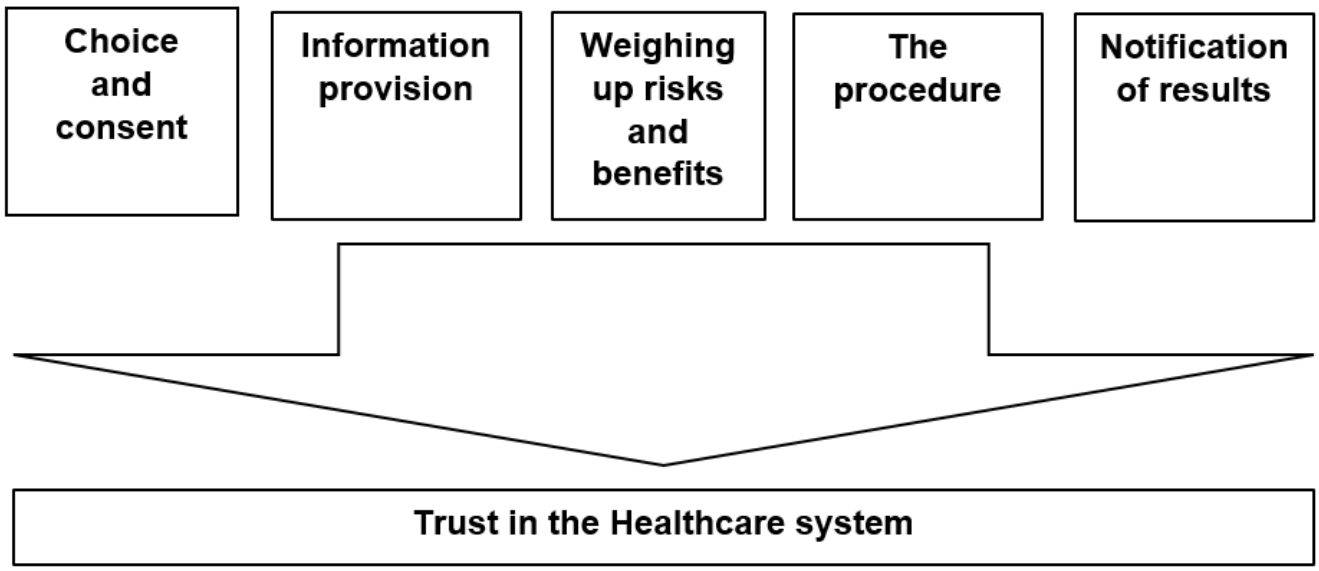


Figure 1: Domains of acceptability

Table 17: Details of studies assessing the acceptability of NBS for SCID

Study	Country	Study Design	Sample Characteristics	Core Themes and additional findings
Blom, 2021[11]	Netherlands	Mixed Methods (Interviews and Questionnaires)	Interviews with parents of newborns with abnormal SCID screening results: 13 mothers, 1 father, 2 both parents Questionnaire sent to 2,000 parents of healthy newborns who participated or declined participation in the Netherlands pilot of NBS screening for SCID, 391 responses (332 who had participated in the NBS screening pilot, 16 who had declined participation and 33 who could not remember whether or not they had participated): Mean age mothers 32.8 years (range 20 to 52 years); 85.8% female	Choice and consent; Information provision; Notification of results; Trust in healthcare system
Blom, 2019[33]	Netherlands	Mixed Methods (Questionnaire)	Questionnaire sent to 4,000 parents of healthy newborns who participated in the Netherlands pilot of NBS screening for SCID, 664 responses: Mean (SD) age mothers 34.7 (4.81) years; mean (SD) age of fathers 32,1 (4.22) years; 86.9% female	Choice and consent; Weighing up risks and benefits; Trust in healthcare system
Howley, 2024[36]	UK	Qualitative (Focus Groups and Written Feedback)	9 families of infants with suspected athymia after NBS screening for SCID: Mixture of mothers, fathers; 14 families of children who were alive and well after the corrective procedure were invited to participate (64% participation rate)	Information provision; Notification of results; Trust in healthcare system Information needs during diagnosis; Communication gaps; Confusion around differential diagnosis
Kutsa, 2022[37]	USA	Qualitative (Interviews)	26 parents of children with SCID or a SCID-like condition, diagnosed through NBS screening: 81% mothers	Notification of results; Trust in healthcare system Parental uncertainties; Coping mechanisms; Trust in medical teams and peer support
Raspa, 2024[35]	USA	Qualitative (Interviews)	26 parents of children with SCID or a SCID-like condition, diagnosed through NBS screening: Mean age 35.1 years; 80.8% mothers	Information provision; Notification of results; Trust in healthcare system

Study	Country	Study Design	Sample Characteristics	Core Themes and additional findings
				Chronic uncertainty; Emotional responses to uncertainty; Need for ongoing support
van Dijk, 2021[34]	Netherlands	Qualitative (Interviews)	Parents who had been offered NBS screening a maximum of 2 years before participation: 17 parents participated; Mean age 33.2 years; 88% female; 5 were parents of children with a normal result, 2 were parents of children with an unspecified FP result and 7 were parents of children with an unspecified TP result	Choice and consent; Notification of results; Trust in healthcare system Benefits and challenges of NBS screening expansion; Parental autonomy; Ethics of screening untreatable conditions

FP: false positive; NBS: newborn blood spot; SCID: severe combined immunodeficiency; SD: standard deviation; TP: true positive

Table 18: Summary pf acceptability findings across the core themes

Study	Choice and Consent	Information Provision	Weighing up risks and benefits	Notification of Results	Trust in Healthcare System
Blom, 2021[11]	Lack of informed choice before screening	Inadequate information from GPs, need for clarity	N/A	Impersonal, rushed telephone results from non-specialists	Overall trust in the NBS screening programme Greater trust in specialists, paediatric immunologists
Blom, 2019[33]	Parental support for screening untreatable conditions	N/A	Early detection (of A-T) was perceived as advantageous; around a quarter of participants sated that they	N/A	Higher trust in newborn screening for providing early diagnosis

Study	Choice and Consent	Information Provision	Weighing up risks and benefits	Notification of Results	Trust in Healthcare System
			could not see any advantages for late detection Majority supported newborn screening for A-T		
Howley, 2024[36]	Gaps in initial communication reduced choice	Delayed and fragmented information caused confusion	N/A	Differential diagnosis introduced late, added anxiety	Trust increased with access to CNS and immunologists
Kutsa, 2022[37]	N/A	N/A	N/A	SCID notification process heightened anxiety	Trust in medical teams was key for parental coping
Raspa, 2024[35]	N/A	Need for ongoing, evolving information throughout SCID journey Emphasis on clarity in consent forms	N/A	Notification delays heightened emotional distress	Trust developed with continued support from specialists
van Dijk, 2021[34]	Call for personalised consent, balancing health gain and ethical concerns	N/A	Overall benefits of the expanded NBS screening programme outweighed negative psychological consequences of certain results (3 parents)	Desire to be informed about incidental findings irrespective of treatability	Stakeholders supported NBS screening expansion if focused on treatable conditions

A-T: ataxia telangiectasia; CNS: clinical nurse specialists; GPs: general practitioners; N/A: not applicable; NBS: newborn blood spot; SCID: severe combined immunodeficiency

Table 19: Parental perspectives on early diagnosis

Study	Advantages of Early Diagnosis	Disadvantages of Early Diagnosis
Blom, 2019[33]	Early diagnosis of untreatable conditions, such as A-T: • Enables families to be medically prepared	Emotional strain for parents who feel they are deprived of the *"golden years"* when the child is healthy

	• Reduces the uncertainty associated with delayed diagnosis • Provides parents with more information to make informed family planning decisions	Potentially unnecessary anxiety over a condition that cannot be treated.
van Dijk, 2021[34]	The role of NBS screening in detecting treatable conditions early was widely supported by stakeholders as helping to prevent delayed health interventions Parents supported NBS screening expansion when it focused on actionable, health-related outcomes	Concerns were raised about expanding screening to include untreatable conditions There were ethical concerns about including untreatable conditions, which could impose emotional burdens on families Some professionals argued that reporting untreatable conditions might lead to unnecessary worry

A-T: ataxia telangiectasia; NBS: newborn blood spot

Table 20: Emotional impact of communication (notification of results)

Study	Method of Communication	Role of Healthcare Professional	Parental Emotional Response
Blom, 2021[11]	Telephone (by non-specialist healthcare providers)	General practitioner; later, paediatric immunologists	Anxiety, distress, long-term emotional strain (especially after false positives)
Howley, 2024[36]	Delayed and fragmented communication; late introduction of differential diagnosis	Non-specialist healthcare providers; paediatric immunologists later	Confusion, distress, anxiety due to delayed communication; use of *'unreliable'* sources for information seeking
Kutsa, 2022[37]	Varied, ongoing communication with healthcare providers	Medical teams and specialists (ongoing)	Ongoing anxiety and distress; emotional coping evolved over time
Raspa, 2024[35]	Telephone (unclear notifications)	Specialists, with some generalist involvement	Heightened emotional distress due to delayed, unclear notifications

Table 21: Parental support needs and reported recommendations for communication

Study	Recommendations for Communication	Support Needs
Blom, 2021[11]	• Clearer explanations when communicating abnormal results • Tandem calls between primary care and specialists • Earlier communication with specialists	• Follow-up care post-referral, psychological support for anxiety • Better clarity during follow-up procedures and ongoing access to specialists

Study	Recommendations for Communication	Support Needs
Howley, 2024[36]	• Early discussion of possible differential diagnoses, especially congenital athymia, to reduce anxiety caused by delays • Ensure caregivers receive detailed, digestible information from the start	• Access to peer networks and CNS • Written and digital resources (roadmap for diagnostics) created with experienced families
Kutsa, 2022[37]	• Clearer communication from healthcare providers about SCID stages and treatment options • Ensure specialists explain treatment pathways early	• Peer support networks, clearer guidance on day-to-day care during diagnostic uncertainty • Access to professional mental health support
Raspa, 2024[35]	• Timely and consistent updates throughout the diagnostic journey to reduce ongoing uncertainty • Clearer explanations from specialists about treatment options	• Regular follow-up care, access to psychological counselling, and emotional support for managing chronic uncertainty
van Dijk, 2021[34]	• Clear, personalised communication especially regarding incidental findings • Inform families about the full implications of NBS screening results and potential outcomes	• Individualised consent processes, peer support groups for emotional and informational guidance • Ongoing healthcare professional support

CNS: clinical nurse specialist; NBS: newborn blood spot; SCID: severe combined immunodeficiency

Table 22: Responses to statements about NBS screening for SCID from parents of healthy newborns

Questionnaire statement	Mean (SD) rating[a]
Parental perceptions of NBS screening for SCID (n=377)[11]	
SCID is a severe disorder and I want this disorder to be detected in my child as early as possible	4.3 (0.90)
I think it is important that SCID is included in the newborn screening programme	4.2 (0.82)
I want to be reassured that my child does not have SCID	3.9 (1.05)
My family/partner wanted the SCID test to be performed for my child	2.7 (1.23)
I only want my child tested for SCID once the pilot study has been completed and SCID has been included in the newborn screening programme	2.2 (1.13)
I think I have a high risk of getting a child with SCID	1.8 (0.87)
The person who performed the heel prick advised me to participate in SCID screening	1.5 (0.81)
Parental perceptions on the detection of A-T through NBS screening for SCID[33]	
Early detection of A-T ensures that a child with A-T can immediately receive optimal guidance when the first symptoms occur	4.5 (0.75)
Early detection of A-T prevents a long period between the first symptoms and the eventual diagnosis	4.2 (0.87)
Early detection of A-T provides parents with the opportunity to make informed choices about family planning	4.2 (0.91)
Early detection of A-T prevents a long period of uncertainty for parents	4.2 (0.99)

Early detection of A-T enables parents to make early adjustments into their lives (for example wheelchair accessible house)	4.3 (0.92)
It is an advantage that parents are informed about the slightly increases risk of developing breast cancer for the mother	4.0 (0.95)
Early detection of A-T ensures that parents can adjust their expectations about the condition of their child	4.0 (0.95)
Early detection of A-T prevents unnecessary additional tests	3.9 (0.93)
Early detection of A-T prevents multiple visits to the hospital	3.6 (1.05)
Early detection of A-T saves extra health costs	3.3 (1.1)
Early detection of A-T ensures that parent can take better care of their child	3.3 (1.24)
Early detection of A-T overburdens parents with information about an untreatable disease during the maternity period	3.4 (1.19)
Early detection of A-T deprives parents of the opportunity to enjoy a seemingly healthy baby in the first months/years of life	3.4 (1.15)
Early detection of A-T makes parents worry about the disease before the symptoms even occur	3.0 (1.16)
Every child has the right to an open future	3.0 (1.16)
Early detection of A-T overburdens parents with information about the increased risk of breast cancer for the mother during the maternity period	2.9 (1.20)
Early detection of A-T adds little to the quality of life of a child with A-T	2.6 (1.06)
The disease A-T cannot be prevented or treated anyway	2.5 (1.14)
You have to take life as it comes	2.5 (1.06)
Early detection of A-T can lead to a reduced bond between parents and child	2.1 (1.18)

[a] Five-point rating scale where 1 = fully disagree and 5 = fully agree
A-T: ataxia telangiectasia; NBS: newborn blood spot; SCID: severe combined immunodeficiency; SD: standard deviation

Table 23: Validation procedures reported in qualitative studies

Study	Study component	Description of validation
Blom, 2021[11]	Interview	Interview items included categorical and non-categorical variables. Non-categorical variables were collected through open questions and were independently keyword-coded by two researchers.
Blom, 2021[11]	Questionnaire	The questionnaire was developed by a multidisciplinary team of experts (newborn screening, medical ethics, survey methods) and qualitatively validated (to address educational and language barriers) in a small test phase (no further details provided). The final version was per reviewed before distribution. Construct validation questions were not included.
Blom, 2019[33]	Questionnaire	The questionnaire was developed by a multidisciplinary team of experts (newborn screening, medical ethics, survey methods). A small test phase was used to check for concept and wording of questions. The open questions were analysed by dividing the answers into categories using a dichotomous variable scoring system. Answers could be assigned to multiple categories and categorisation was undertaken by two researchers, independently.

Howley, 2024[36]	Video call or written feedback	None reported.
Kutsa, 2022[37]	Interview	Interviews were conducted by two researchers with experience in qualitative research methodology. A semi-structured interview guide was used. The research team included coders interviewers, senior researchers with expertise in newborn screening and rare diseases, health behaviour and uncertainties. Inductive content analysis was used and coding was refined through discussion during double coding of the first six interview transcripts. Three additional transcripts were double coded at intervals.
Raspa, 2024[35]	Interview	Interviewers took extensive notes using a structured template and interviews were recorded and transcribed using a cloud services. A combination of deductive and inductive content analysis was used to describe parents' responses to uncertainty. The multi-disciplinary research team (coders, interviewers, senior researchers with expertise in newborn screening and health behaviour) developed the initial list of codes. The first six interview transcripts were double-coded and any unclear codes were discussed and refined. Two addition transcripts were then double-coded to check inter-rater reliability and three further transcripts were double coded at intervals through the study.
van Dijk, 2021[34]	Interview	Separate interview guides were developed for parents and professionals. Interviews were audio recorded and transcribed verbatim. Thematic analysis was done in parallel with interviewing and interviews were coded using inductive coding, by two researchers independently. Researchers were trained and experienced with qualitative research. The two researchers independently generated code trees and compared their ways of coding after three interviews. Based on these two conceptual code trees a definitive code tree was developed for use in the remaining interviews. After six interviews, the way of coding was again compared and discussed and differences discussed until consensus was reached.

Review summary

Conclusions and implications for policy

This evidence summary employed standard systematic review methodology to ensure that the capture of relevant evidence was as complete as possible. In addition, to provide further context, this report includes vignettes of some non-SCID TCL conditions that may be identified by NBS screening for SCID, a summary of the current status of NBS screening programmes for SCID internationally and findings from the results of horizon scanning for developments in gene therapy for SCID.

The key areas of uncertainty remain those which concern how the identification of non-SCID TCL, through screening, should be handled. For many non-SCID TCL conditions, treatment options remain limited and long-term prognosis unclear.

The systematic review component of this evidence summary was limited by a restriction to full publications in English. This may have resulted in an incomplete picture, particularly in respect of the details of implemented NBS screening programmes for SCID internationally.

Criterion 4, *'There should be a simple, safe, precise and validated screening test,'* was considered to be partially met by the 2017 UK NSC evidence summary. This conclusion is primarily driven by the effects of non-SCID (incidental) findings on the PPV of the TREC test. Subsequent evidence, particularly from screening programmes in the US, indicates that the use of screening algorithms that include repeat sampling (e.g. at term-adjusted gestational age) in preterm babies can markedly reduce FP results due to transient TCL of prematurity. However, even where FP results due to prematurity are reduced or eliminated, the large number of other conditions that can give rise to a low TREC value (positive screening result) mean that the PPV for SCID remains consistently poor. There remains uncertainty about how the identification of non-SCID TCL conditions by screening should be handled, particularly where treatment options remain limited and long-term prognosis unclear. Whether or not criterion 4 is considered to be met is therefore likely to be substantially dependent upon how non-SCID TCLs (incidental findings) are treated.

Criterion 5, '*The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed,'* was considered to be met following the previous (2017) evidence review. There has been no change to the evidence base, as no data is yet available from the ISE of newborn screening for SCID conducted in the NHS in England.

Findings from the ISE may provide more up to date information on test and cut-off values from a large UK sample (criterion 5). The ISE also has the potential to provide UK-specific insights into how incidental findings have been handled in practice, including care pathways and outcomes for these children and their families (criterion 4).

The 2017 evidence review concluded that the criterion, *'there should be an effective treatment with evidence that early treatment improves prognosis,'* was met. This evidence summary strengthens that conclusion by including robust evidence that early diagnosis through NBS screening is associated with improved post-transplant survival for SCID patients and that this effect is likely to be driven by earlier and transplant and reduced infection burden. We therefore consider that criterion 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,' is met for screening-detected SCID. However, for many non-SCID conditions, treatment options remain limited and long-term prognosis unclear. Evaluating the harms and benefits resulting from screen detection of non-SCID conditions is a methodological challenge both for the non-SCID cases themselves and for gauging the balance of benefits and harms of NBS for SCID.

Criterion 6, '*The test, from sample collection to delivery of results, should be acceptable to the target population,'* has not been considered in previous evidence reviews. The findings of this evidence summary were broadly indicative of parental support for NBS screening for SCID. There was also some evidence that parents regarded the early identification of non-SCID conditions (incidental findings) as advantageous irrespective of treatability and that there was support for reporting of such findings. However, there remains a paucity of evidence derived from parents who have experienced a positive result on NBS screening for SCID and in particular those who have experienced a positive screening result and a subsequent non-SCID diagnosis (incidental finding). We therefore consider that, whilst there is some evidence of parental support for NBS screening for SCID and for the early identification of non-SCID conditions (incidental findings), further work (e.g. stakeholder dialogue Patient and Public Involvement activities) may be helpful to establish whether criterion 6, *'the test, from sample collection to delivery of results, should be acceptable to the target population,'* is met.

The current published evidence base alone is not adequate to fully support implementation of NBS screening for SCID.

The findings of this evidence summary should be considered alongside findings from the ISE of newborn screening for SCID conducted in the NHS in England and the results of cost-effectiveness modelling.

Further work is needed to establish how the identification of non-SCID TCL conditions by screening should be handled. Stakeholder dialogue and Patient and Public Involvement activities may be helpful. In particular, the views of parents who have lived experience of a non-SCID (incidental) finding from NBS screening for SCID should be sought.

Appendix 1 — Search strategy

Electronic databases

The searches included searches of the databases shown in Table 24. MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print, Embase, CINAHL, PsycINFO, The Cochrane Library (CDSR and CENTRAL), the International HTA Database, KSR Evidence.

Table 24: Databases searched

Resource	Host	Date range	Date searched	Records found	Records found after deduplication
MEDLINE	Ovid	1946 to April 15, 2024	17.4.24	1371	1,305
EMBASE	Ovid	1974 to 2024 April 16	17.4.24	2194	1,100
CINAHL	EBSCO	2011 to 16.4.24	16.4.24	232	51
PsycINFO	Ovid	1806 to April Week 1 2024	17.4.24	30	21
CDSR	Wiley	Issue 4 of 12, April 2024	16.4.24	5	5
CENTRAL	Wiley	Issue 3 of 12, March 2024	16.4.24	71	22
International HTA Database	https://database.inahta.org/	2011 to 16.4.24	16.4.24	11	7
KSR Evidence	https://ksrevidence.com/	to 16.4.24	16.4.24	12	6

Search Terms

Search terms included combinations of free text and subject headings (MeSH for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: SCID
- intervention: Newborn screening
- Intervention: Treatments

Search terms for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print shown in Table 25, search terms for Embase are shown in Table 26, search terms for the Cochrane Library databases are shown in Table 27, search terms for CINAHL databases are shown in Table 28, search terms for PsycINFO are shown in Table 29, search terms for the International HTA Database are shown in Table 30 and search terms for KSR Evidence are shown in Table 31.

Table 25: Search strategy for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print

Term Group	#	Search terms	Results
Disease	1	exp Severe Combined Immunodeficiency/	4,558
	2	(severe combined adj2 (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab,ot,hw.	8,790
	3	((SCID or SCIDs) and (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab,ot,hw.	5,576
	4	bare lymphocyte syndrome$.ti,ab,ot,hw.	161
	5	familial reticuloendothelios$.ti,ab,ot,hw.	10
	6	Omenn$ syndrome$.ti,ab,ot,hw.	320
	7	Swiss-type agammaglobulin?emia.ti,ab,ot,hw.	8
	8	Alymphocytosis.ti,ab,ot,hw.	28
	9	(severe mixed adj2 (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab,ot,hw.	1
	10	Glanzmann-Riniker syndrome$.ti,ab,ot,hw.	1
	11	Thymic alymphoplasia.ti,ab,ot,hw.	37
	12	(adenosine deaminase deficiency or ADA deficiency).ti,ab,ot,hw.	708
	13	(purine nucleoside phosphorylase deficiency or PNP deficiency).ti,ab,ot,hw.	217
	14	Reticular dysgenesis.ti,ab,ot,hw.	67
	15	JAK3 deficiency.ti,ab,ot,hw.	29
	16	(DCLRE1C or PRKDC).ti,ab,ot,hw.	578
	17	(bubble boy disease or bubble baby disease).ti,ab,ot,hw.	7
	18	(x linked adj3 (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab,ot,hw.	1,245

	19	(XSCID or SCIDX or SCIDX1).ti,ab,ot,hw.	125
	20	("immunodeficiency 4" or "immunodeficiency 6").ti,ab,ot,hw.	20
	21	or/1-20	11,531
Intervention (screening)	22	Neonatal Screening/	12,178
	23	exp Infant/ and exp Mass Screening/	21,609
	24	((neonatal$ or newborn$ or infant$ or baby or babies) adj3 (screen$ or test$ or diagnos$)).ti,ab,ot,hw.	44,218
	25	(heelprick$ or heel prick$).ti,ab,ot,hw.	445
	26	Dried Blood Spot Testing/	2,143
	27	(blood spot$ or bloodspot$ or NBS).ti,ab,ot,hw.	15,103
	28	((dried or dry) adj1 (blood test$ or blood sampl$)).ti,ab,ot,hw.	521
	29	Guthrie.ti,ab,ot,hw.	826
	30	(T-cell receptor excision circle$ or TRECs or TREC).ti,ab,ot,hw.	1,279
	31	(EnLite$ or PerkinElmer or Eonis$ or "Immuno IVD SPOT-it$" or "SCREEN-ID").ti,ab,ot,hw.	335
	32	(Kappa deleting recombination excision circle$ or KREC or KRECs).ti,ab,ot,hw.	146
	33	(genetic adj3 (screen$ or test$ or diagnos$)).ti,ab,ot,hw.	132,689
	34	or/22-33	195,524
	35	21 and 34	825
Intervention (treatment)	36	exp Hematopoietic Stem Cell Transplantation/	59,077
	37	(h?ematopoietic stem cell therap$ or HSC therap$).ti,ab,ot,hw.	144
	38	(h?ematopoietic stem cell transplant$ or HSC transplant$).ti,ab,ot,hw.	67,105
	39	(HPSCT or HSCT).ti,ab,ot,hw.	17,247
	40	Bone Marrow Transplantation/	45,809
	41	(bone marrow adj2 (transplant$ or transfer$ or graft$ or transfusion$)).ti,ab,ot,hw.	59,717
	42	exp Genetic Therapy/	54,526
	43	((gene or genes or genetic$ or genom$) adj2 (therap$ or treatment$ or transfer$ or edit$ or modif$)).ti,ab,ot,hw.	271,155
	44	(strimvelis$ or "gsk 2696273" or "gsk2696273").ti,ab,ot,hw.	24
	45	((thymic or thymus) adj2 (transplant$ or graft$)).ti,ab,ot,hw.	1,009
	46	or/36-45	391,742
	47	21 and 46	3,090
	48	35 or 47	3,653
	49	exp animals/ not (exp animals/ and humans/)	5,212,238
	50	(letter or editorial or note or preprint).pt.	1,958,886
	51	48 not (49 or 50)	3,216
	52	**limit 51 to yr="2011 -Current"**	**1,371**

Table 26: Search strategy for Embase (Searched via Ovid)

Term Group	#	Search terms	Results
Disease	1	exp severe combined immunodeficiency/	8,147
	2	(severe combined adj2 (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab,ot,hw.	11,632
	3	((SCID or SCIDs) and (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab,ot,hw.	10,209
	4	bare lymphocyte syndrome$.ti,ab,ot,hw.	532
	5	familial reticuloendothelios$.ti,ab,ot,hw.	4
	6	Omenn$ syndrome$.ti,ab,ot,hw.	827
	7	Swiss-type agammaglobulin?emia.ti,ab,ot,hw.	5
	8	Alymphocytosis.ti,ab,ot,hw.	11
	9	(severe mixed adj2 (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab,ot,hw.	1
	10	Glanzmann-Riniker syndrome$.ti,ab,ot,hw.	0
	11	Thymic alymphoplasia.ti,ab,ot,hw.	10
	12	(adenosine deaminase deficiency or ADA deficiency).ti,ab,ot,hw.	1,813
	13	(purine nucleoside phosphorylase deficiency or PNP deficiency).ti,ab,ot,hw.	336
	14	Reticular dysgenesis.ti,ab,ot,hw.	153
	15	JAK3 deficiency.ti,ab,ot,hw.	110
	16	(DCLRE1C or PRKDC).ti,ab,ot,hw.	1,441
	17	(bubble boy disease or bubble baby disease).ti,ab,ot,hw.	6
	18	(x linked adj3 (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab,ot,hw.	1,887
	19	(XSCID or SCIDX or SCIDX1).ti,ab,ot,hw.	178
	20	("immunodeficiency 4" or "immunodeficiency 6").ti,ab,ot,hw.	59
	21	or/1-20	19,211
Intervention (screening)	22	newborn screening/	23,867
	23	exp infant/ and exp screening/	42,766
	24	((neonatal$ or newborn$ or infant$ or baby or babies) adj3 (screen$ or test$ or diagnos$)).ti,ab,ot,hw.	64,311
	25	(heelprick$ or heel prick$).ti,ab,ot,hw.	644
	26	dried blood spot testing/	6,652
	27	(blood spot$ or bloodspot$ or NBS).ti,ab,ot,hw.	23,121
	28	((dried or dry) adj1 (blood test$ or blood sampl$)).ti,ab,ot,hw.	733
	29	Guthrie.ti,ab,ot,hw.	1,102
	30	t-cell receptor excision circle test kit/	35

	31	(T-cell receptor excision circle$ or TRECs or TREC).ti,ab,ot,hw.	2,148
	32	(EnLite$ or PerkinElmer or Eonis$ or "Immuno IVD SPOT-it$" or "SCREEN-ID").ti,ab,ot,hw.	1,481
	33	(Kappa deleting recombination excision circle$ or KREC or KRECs).ti,ab,ot,hw.	319
	34	(genetic adj3 (screen$ or test$ or diagnos$)).ti,ab,ot,hw.	190,297
	35	or/22-34	286,358
	36	21 and 35	1,824
Intervention (treatment)	37	exp hematopoietic stem cell transplantation/	92,372
	38	(h?ematopoietic stem cell therap$ or HSC therap$).ti,ab,ot,hw.	212
	39	(h?ematopoietic stem cell transplant$ or HSC transplant$).ti,ab,ot,hw.	105,322
	40	(HPSCT or HSCT).ti,ab,ot,hw.	40,725
	41	exp bone marrow transplantation/	71,995
	42	(bone marrow adj2 (transplant$ or transfer$ or graft$ or transfusion$)).ti,ab,ot,hw.	83,539
	43	exp gene therapy/	102,848
	44	((gene or genes or genetic$ or genom$) adj2 (therap$ or treatment$ or transfer$ or edit$ or modif$)).ti,ab,ot,hw.	291,703
	45	strimvelis/	133
	46	(strimvelis$ or "gsk 2696273" or "gsk2696273").ti,ab,ot,hw.	165
	47	exp thymus transplantation/	901
	48	((thymic or thymus) adj2 (transplant$ or graft$)).ti,ab,ot,hw.	1,470
	49	or/37-48	476,516
	50	21 and 49	5,661
	51	36 or 50	6,760
	52	animal/	1,655,307
	53	animal experiment/	3,138,118
	54	(rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw.	7,810,948
	55	or/52-54	7,810,948
	56	exp human/	26,412,187
	57	human experiment/	658,204
	58	or/56-57	26,414,791
	59	55 not (55 and 58)	5,832,107
	60	51 not 59	6,126
	61	("conference abstract" or "conference review").pt. or conference$.so,st.	5,172,891
	62	60 not 61	4,480
	63	(letter or editorial or note or preprint).pt.	3,216,732
	64	62 not 63	4,033

	65	**limit 64 to yr="2011 -Current"**	**2,194**

Table 27: Search strategy for CDSR and CENTRAL (Searched via The Cochrane Library [Wiley])

Term Group	#	Search terms	Results
Disease	#1	MeSH descriptor: [Severe Combined Immunodeficiency] explode all trees	11
	#2	"severe combined" near/2 (immunodeficienc* or (immuno next deficienc*) or (immune next deficienc*) or (immunologic next deficienc*))	69
	#3	(SCID or SCIDs) and (immunodeficienc* or (immuno next deficienc*) or (immune next deficienc*) or (immunologic next deficienc*))	63
	#4	bare next lymphocyte next syndrome*	0
	#5	familial next reticuloendothelios*	0
	#6	Omenn* next syndrome*	1
	#7	"Swiss-type agammaglobulinemia" or "Swiss-type agammaglobulinaemia"	0
	#8	Alymphocytosis	0
	#9	"severe mixed" near/2 (immunodeficienc* or (immuno next deficienc*) or (immune next deficienc*) or (immunologic next deficienc*))	0
	#10	Glanzmann next Riniker next syndrome*	0
	#11	"Thymic alymphoplasia"	0
	#12	"adenosine deaminase deficiency" or "ADA deficiency"	7
	#13	"purine nucleoside phosphorylase deficiency" or "PNP deficiency"	1
	#14	"Reticular dysgenesis"	0
	#15	"JAK3 deficiency"	0
	#16	DCLRE1C or PRKDC	5
	#17	"bubble boy disease" or "bubble baby disease"	0
	#18	"x linked" near/3 (immunodeficienc* or (immuno next deficienc*) or (immune next deficienc*) or (immunologic next deficienc*))	22
	#19	XSCID or SCIDX or SCIDX1	2
	#20	"immunodeficiency 4" or "immunodeficiency 6"	1
	#21	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 with Cochrane Library publication date Between Jan 2011 and Apr 2024, in Cochrane Reviews	5
	#22	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 with Publication Year from 2011 to 2024, in Trials	71

Table 28: Search strategy for CINAHL (Searched via EBSCO)

Term Group	#	Search terms	Results
Disease	S1	(MH "Severe Combined Immunodeficiency")	521
	S2	TI ("severe combined" N2 (immunodeficienc* or "immuno deficienc*" or "immune deficienc*" or "immunologic deficienc*")) OR AB ("severe combined" N2 (immunodeficienc* or "immuno deficienc*" or "immune deficienc*" or "immunologic deficienc*"))	479
	S3	TI ((SCID or SCIDs) and (immunodeficienc* or "immuno deficienc*" or "immune deficienc*" or "immunologic deficienc*")) OR AB ((SCID or SCIDs) and (immunodeficienc* or "immuno deficienc*" or "immune deficienc*" or "immunologic deficienc*"))	239
	S4	TI "bare lymphocyte syndrome*" OR AB "bare lymphocyte syndrome*"	6
	S5	TI "familial reticuloendothelios*" OR AB "familial reticuloendothelios*"	0
	S6	TI "Omenn* syndrome*" OR AB "Omenn* syndrome*"	22
	S7	TI "Swiss-type agammaglobulin#emia" OR AB "Swiss-type agammaglobulin#emia"	0
	S8	TI Alymphocytosis OR AB Alymphocytosis	0
	S9	TI ("severe mixed" N2 (immunodeficienc* or "immuno deficienc*" or "immune deficienc*" or "immunologic deficienc*")) OR AB ("severe mixed" N2 (immunodeficienc* or "immuno deficienc*" or "immune deficienc*" or "immunologic deficienc*"))	0
	S10	TI "Glanzmann-Riniker syndrome*" OR AB "Glanzmann-Riniker syndrome*"	0
	S11	TI "Thymic alymphoplasia" OR AB "Thymic alymphoplasia"	0
	S12	TI ("adenosine deaminase deficiency" or "ADA deficiency") OR AB ("adenosine deaminase deficiency" or "ADA deficiency")	45
	S13	TI ("purine nucleoside phosphorylase deficiency" or "PNP deficiency") OR AB ("purine nucleoside phosphorylase deficiency" or "PNP deficiency")	14
	S14	TI "Reticular dysgenesis" OR AB "Reticular dysgenesis"	4
	S15	TI "JAK3 deficiency" OR AB "JAK3 deficiency"	4
	S16	TI (DCLRE1C or PRKDC) OR AB (DCLRE1C or PRKDC)	41
	S17	TI ("bubble boy disease" or "bubble baby disease") OR AB ("bubble boy disease" or "bubble baby disease")	0
	S18	TI ("x linked" N3 (immunodeficienc* or "immuno deficienc*" or "immune deficienc*" or	91

		"immunologic deficienc*")) OR AB ("x linked" N3 (immunodeficienc* or "immuno deficienc*" or "immune deficienc*" or "immunologic deficienc*"))	
	S19	TI (XSCID or SCIDX or SCIDX1) OR AB (XSCID or SCIDX or SCIDX1)	0
	S20	TI ("immunodeficiency 4" or "immunodeficiency 6") OR AB ("immunodeficiency 4" or "immunodeficiency 6")	0
	S21	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	901
	S22	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 [includes 2011+ publication year limit]	578
Intervention (screening)	S23	(MH "Neonatal Assessment+")	9,105
	S24	(MH "Infant+") AND (MH "Health Screening+")	10,155
	S25	TI ((neonatal* or newborn* or infant* or baby or babies) N3 (screen* or test* or diagnos*)) OR AB ((neonatal* or newborn* or infant* or baby or babies) N3 (screen* or test* or diagnos*))	12,957
	S26	TI (heelprick* or "heel prick*") OR AB (heelprick* or "heel prick*")	144
	S27	TI ("blood spot*" or bloodspot* or NBS) OR AB ("blood spot*" or bloodspot* or NBS)	1,899
	S28	TI ((dried or dry) N1 ("blood test*" or "blood sampl*")) OR AB ((dried or dry) N1 ("blood test*" or "blood sampl*"))	77
	S29	TI Guthrie OR AB Guthrie	149
	S30	TI ("T-cell receptor excision circle*" or TRECs or TREC) OR AB ("T-cell receptor excision circle*" or TRECs or TREC)	241
	S31	TI (EnLite* or PerkinElmer or Eonis* or "Immuno IVD SPOT-it*" or "SCREEN-ID") OR AB (EnLite* or PerkinElmer or Eonis* or "Immuno IVD SPOT-it*" or "SCREEN-ID")	82
	S32	TI ("Kappa deleting recombination excision circle*" or KREC or KRECs) OR AB ("Kappa deleting recombination excision circle*" or KREC or KRECs)	19
	S33	TI (genetic N3 (screen* or test* or diagnos*)) OR AB (genetic N3 (screen* or test* or diagnos*))	16,166
	S34	S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33	41,412
Intervention (treatment)	S35	(MH "Hematopoietic Stem Cell Transplantation")	10,430

	S36	TI ("h#ematopoietic stem cell therap*" or "HSC therap*") OR AB ("h#ematopoietic stem cell therap*" or "HSC therap*")	20
	S37	TI ("h#ematopoietic stem cell transplant*" or "HSC transplant*") OR AB ("h#ematopoietic stem cell transplant*" or "HSC transplant*")	5,956
	S38	TI (HPSCT or HSCT) OR AB (HPSCT or HSCT)	2,715
	S39	(MH "Bone Marrow Transplantation+")	4,883
	S40	TI ("bone marrow" N2 (transplant* or transfer* or graft* or transfusion*)) OR AB ("bone marrow" N2 (transplant* or transfer* or graft* or transfusion*))	3,816
	S41	(MH "Gene Therapy")	5,283
	S42	TI ((gene or genes or genetic* or genom*) N2 (therap* or treatment* or transfer* or edit* or modif*)) OR AB ((gene or genes or genetic* or genom*) N2 (therap* or treatment* or transfer* or edit* or modif*))	13,403
	S43	TI ((strimvelis* or "gsk 2696273" or "gsk2696273")) OR AB ((strimvelis* or "gsk 2696273" or "gsk2696273"))	1
	S44	TI ((thymic or thymus) N2 (transplant* or graft*)) OR AB ((thymic or thymus) N2 (transplant* or graft*))	33
	S45	S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44	33,651
	S46	S22 AND S34	131
	S47	S22 AND S45	135
	S48	S46 OR S47 [includes 2011+ publication year limit]	232

Table 29: Search strategy for PsycINFO (Searched via Ovid)

Term Group	#	Search terms	Results
Disease	1	(severe combined adj2 (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab.	43
	2	((SCID or SCIDs) and (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab.	39
	3	bare lymphocyte syndrome$.ti,ab.	0
	4	familial reticuloendothelios$.ti,ab.	0
	5	Omenn$ syndrome$.ti,ab.	1
	6	Swiss-type agammaglobulin?emia.ti,ab.	0
	7	Alymphocytosis.ti,ab.	1
	8	(severe mixed adj2 (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab.	0
	9	Glanzmann-Riniker syndrome$.ti,ab.	0
	10	Thymic alymphoplasia.ti,ab.	0

	11	(adenosine deaminase deficiency or ADA deficiency).ti,ab.	0
	12	(purine nucleoside phosphorylase deficiency or PNP deficiency).ti,ab.	0
	13	Reticular dysgenesis.ti,ab.	0
	14	JAK3 deficiency.ti,ab.	0
	15	(DCLRE1C or PRKDC).ti,ab.	8
	16	(bubble boy disease or bubble baby disease).ti,ab.	0
	17	(x linked adj3 (immunodeficienc$ or immuno deficienc$ or immune deficienc$ or immunologic deficienc$)).ti,ab.	2
	18	(XSCID or SCIDX or SCIDX1).ti,ab.	0
	19	("immunodeficiency 4" or "immunodeficiency 6").ti,ab.	0
	20	or/1-19	66
	21	**limit 20 to yr="2011 -Current"**	**30**

Table 30: Search strategy for the International HTA Database (searched via https://database.inahta.org/)

Term Group	#	Search terms	Results
Disease	1	"Severe Combined Immunodeficiency"[mhe]	9
	2	severe combined immunodeficienc*	10
	3	severe combined immuno deficienc*	0
	4	severe combined immune deficienc*	3
	5	severe combined immunologic deficienc*	0
	6	SCID or SCIDs	5
	7	bare lymphocyte syndrome*	0
	8	familial reticuloendothelios*	0
	9	Omenn* syndrome*	0
	10	Swiss-type agammaglobulinemia or Swiss-type agammaglobulinaemia	0
	11	Alymphocytosis	0
	12	severe mixed immunodeficienc*	0
	13	severe mixed immuno deficienc*	0
	14	severe mixed immune deficienc*	0
	15	severe mixed immunologic deficienc*	0
	16	Glanzmann Riniker syndrome*	0
	17	Thymic alymphoplasia	0
	18	"adenosine deaminase deficiency" or "ADA deficiency"	2
	19	purine nucleoside phosphorylase deficiency or "PNP deficiency"	0
	20	Reticular dysgenesis	0
	21	JAK3 deficiency	0
	22	DCLRE1C or PRKDC	0
	23	"bubble boy disease" or "bubble baby disease"	0
	24	"x linked immunodeficienc* "	0
	25	"x linked immune deficienc*"	0

	26	"x linked immunologic deficienc*"	0
	27	XSCID or SCIDX or SCIDX1	0
	28	"immunodeficiency 4" or "immunodeficiency 6"	0
	29	#28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	11

Table 31: Search strategy for KSR Evidence (searched via https://ksrevidence.com/)

Term Group	#	Search terms	Results
Disease	1	"severe combined" adj2 (immunodeficienc* or "immuno deficienc*" or "immune deficienc*" or "immunologic deficienc*") in All text	10 results
	2	(SCID or SCIDs) and (immunodeficienc* or "immuno deficienc*" or "immune deficienc*" or "immunologic deficienc*") in All text	7 results
	3	"bare lymphocyte syndrome*" in All text	0 results
	4	"familial reticuloendothelios*" in All text	0 results
	5	"Omenn* syndrome*" in All text	0 results
	6	"Swiss-type agammaglobulin?emia" in All text	0 results
	7	Alymphocytosis in All text	0 results
	8	"severe mixed" adj2 (immunodeficienc* or "immuno deficienc*" or "immune deficienc*" or "immunologic deficienc*") in All text	0 results
	9	"Glanzmann-Riniker syndrome*" in All text	0 results
	10	"Thymic alymphoplasia" in All text	0 results
	11	"adenosine deaminase deficiency" or "ADA deficiency" in All text	0 results
	12	"purine nucleoside phosphorylase deficiency" or "PNP deficiency" in All text	0 results
	13	"Reticular dysgenesis" in All text	0 results
	14	"JAK3 deficiency" in All text	0 results
	15	DCLRE1C or PRKDC in All text	0 results
	16	"bubble boy disease" or "bubble baby disease" in All text	0 results
	17	"x linked" adj3 (immunodeficienc* or "immuno deficienc*" or "immune deficienc*" or "immunologic deficienc*") in All text	1 result
	18	XSCID or SCIDX or SCIDX1 in All text	0 results
	19	"immunodeficiency 4" or "immunodeficiency 6" in All text	0 results
	20	**#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #18 or #17 or #19 in All text**	**12 results**

Results were imported into EndNote and duplicates removed.

Additional vignette searches

The searches for the vignettes included searches of the databases shown in Table 32. Trip, GIN, NICE, NIHR HTA, ECRI, Policy Commons, ScanMedicine, Orphanet, CDSR, International HTA Database, KSR Evidence, ClinicalTrials.gov, ICTRP, EU Clinical Trials Register

Table 32: Vignettes searches

Horizon Scanning/Vignettes	Host	Date range	Date searched	Records found	Records found after deduplication
Trip	https://www.tripdatabase.com/	2017 to 8.5.24	8.5.24	183	160
GIN	https://g-i-n.net/international-guidelines-library/	2017 to 8.5.24	8.5.24	11	11
NICE	https://www.nice.org.uk/	2017 to 8.5.24	8.5.24	2	2
NIHR HTA	https://www.nihr.ac.uk/	2017 to 8.5.24	8.5.24	3	3
ECRI	https://guidelines.ecri.org/	2017 to 8.5.24	8.5.24	0	0
Policy Commons	https://policycommons.net/	2017 to 8.5.24	8.5.24	33	5
ScanMedicine	https://scanmedicine.com/	2017 to 8.5.24	8.5.24	1	1
Orphanet	https://nbs.orphanet.app/	2017 to 8.5.24	8.5.24	4	4
CDSR	Wiley	2017 to 8.5.24	8.5.24	1	0
International HTA Database (Internet)	https://database.inahta.org/	2017 to 8.5.24	8.5.24	1	0
KSR Evidence (Internet)	https://ksrevidence.com/	2017 to 8.5.24	8.5.24	43	43
Trials registers					
ClinicalTrials.gov	https://clinicaltrials.gov/	2017 to 29.5.24	29.5.24 8.7.24	70	
ICTRP	https://trialsearch.who.int/	2017 to 29.5.24	29.5.24 8.7.24	35	

EU Clinical Trials Register	https://www.clinicaltrialsregister.eu/	2017 to 29.5.24	29.5.24 8.7.24	8	
TOTAL				**4,239**	**2,777**

Search Terms

Search terms included combinations of free text and subject headings (MeSH for MEDLINE) where available, focussing on the following three areas of interest.

- DiGeorge Syndrome
- Ataxia Telangiectasia
- DOCK8

Trip Database
https://www.tripdatabase.com/
Date searched: 8.5.24
Records found: 160

Limit: 2017+

Search term	Results
((("severe combined immunodeficiency") OR ("severe combined immuno deficiency") OR (scid)) OR ("adenosine deaminase deficiency") OR ("ada deficiency")) AND (((gsk2696273) OR ("gsk 2696273") OR (strimvelis)) OR (("gene therapy") OR ("genetic therapy") OR ("gene treatment") OR ("genetic treatment") OR ("gene modification") OR ("genetic modification")))from_date:2017 to_date:2024	Guidelines: 15 Regulatory Guidance: 1 Evidence Based Synopses: 7
(("digeorge syndrome") OR ("di george syndrome") OR ("autosomal dominant opitz g bbb syndrome") OR ("22q11 deletion syndrome") OR ("22q11.2 deletion syndrome") OR ("conotruncal anomaly face syndrome")) from_date:2017 to_date:2024	Guidelines: 68 Regulatory Guidance: 0 Evidence Based Synopses: 14
(("louis bar disease") OR ("bar syndrome") OR ("ataxia telangiectasia")) from_date:2017 to_date:2024	Guidelines: 35 Regulatory Guidance: 4 Evidence Based Synopses: 16
(("dock8") OR ("dock 8") OR ("dedicator of cytokinesis protein 8") OR ("autosomal recessive hies") OR ("arhies") OR ("hyper immunoglobulin e") OR ("hyper ige") OR ("hyperimmunoglobulin e")) from_date:2017 to_date:2024	Guidelines: 21 Regulatory Guidance: 0 Evidence Based Synopses: 2
TOTAL BEFORE DEDUPLICATION	**183**
TOTAL AFTER DEDUPLICATION	**160**

International Guidelines Library
https://g-i-n.net/international-guidelines-library/
Date searched: 8.5.24
Records found:

Limit: 2017+

Search term	Results
"severe combined immuno deficiency" or "severe combined immunodefi-ciency" or SCID or "adenosine deaminase deficiency" or "ada deficiency"	5
"digeorge syndrome" or "di george syndrome" or "autosomal dominant opitz g bbb syndrome" or "22q11 deletion syndrome" or "22q11.2 deletion syn-drome"	1
"louis bar disease" or "bar syndrome" or "ataxia telangiectasia"	4
" dock8" or " dock 8" or " dedicator of cytokinesis protein 8" or " autosomal recessive hies" or " ar-hies" or "hyper immunoglobulin e" or "hyper ige" or "hyperimmunoglobulin e"	1
TOTAL BEFORE DEDUPLICATION	**11**
TOTAL AFTER DEDUPLICATION	**11**

National Institute for Health and Care Excellence (NICE)
https://www.nice.org.uk/
Date searched: 8.5.24
Records found: 2

Limit: 2017+

Search term	Results
"severe combined immuno deficiency" or "severe combined immunodefi-ciency" or SCID or "adenosine deaminase deficiency" or "ada deficiency"	2
"digeorge syndrome" or "di george syndrome" or "autosomal dominant opitz g bbb syndrome" or "22q11 deletion syndrome" or "22q11.2 deletion syn-drome"	0
"louis bar disease" or "bar syndrome" or "ataxia telangiectasia"	0
" dock8" or " dock 8" or " dedicator of cytokinesis protein 8" or " autosomal recessive hies" or " ar-hies" or "hyper immunoglobulin e" or "hyper ige" or "hyperimmunoglobulin e"	0
TOTAL BEFORE DEDUPLICATION	**2**
TOTAL AFTER DEDUPLICATION	**2**

National Institute for Health and Care Research
https://www.nihr.ac.uk/
Date searched: 8.5.24
Records found: 3

Limit: 2017+

Search term	Results
"severe combined immuno deficiency" or "severe combined immunodefi-ciency" or SCID or "adenosine deaminase deficiency" or "ada deficiency"	1
"digeorge syndrome" or "di george syndrome" or "autosomal dominant opitz g bbb syndrome" or "22q11 deletion syndrome" or "22q11.2 deletion syn-drome"	0
"louis bar disease" or "bar syndrome" or "ataxia telangiectasia"	2
" dock8" or " dock 8" or " dedicator of cytokinesis protein 8" or " autosomal recessive hies" or " ar-hies" or "hyper immunoglobulin e" or "hyper ige" or "hyperimmunoglobulin e"	0
TOTAL BEFORE DEDUPLICATION	**3**
TOTAL AFTER DEDUPLICATION	**3**

ECRI Guidelines Trust
https://guidelines.ecri.org/
Date searched: 8.5.24
Records found: 0

Limit: 2017+

Search term	Results
"severe combined immuno deficiency" or "severe combined immunodefi-ciency" or SCID or "adenosine deaminase deficiency" or "ada deficiency"	0
"digeorge syndrome" or "di george syndrome" or "autosomal dominant opitz g bbb syndrome" or "22q11 deletion syndrome" or "22q11.2 deletion syn-drome"	0
"louis bar disease" or "bar syndrome" or "ataxia telangiectasia"	0
" dock8" or " dock 8" or " dedicator of cytokinesis protein 8" or " autosomal recessive hies" or " ar-hies" or "hyper immunoglobulin e" or "hyper ige" or "hyperimmunoglobulin e"	0
TOTAL BEFORE DEDUPLICATION	**0**
TOTAL AFTER DEDUPLICATION	**0**

Policy Commons
https://policycommons.net/
Date searched: 8.5.24
Records found: 31

Limit: 2017+

Search term	Results
("severe combined immuno deficiency" OR "severe combined immunodeficiency" OR SCID OR "adenosine deaminase deficiency" OR "ada deficiency") AND (gsk2696273 OR "gsk 2696273" OR strimvelis OR "gene therapy" OR "genetic therapy" OR "gene treatment" OR "genetic treatment" OR "gene modification" OR "genetic modification")	27
"digeorge syndrome" OR "di george syndrome" OR "autosomal dominant opitz g bbb syndrome" OR "22q11 deletion syndrome" OR "22q11.2 deletion syndrome"	3
"louis bar disease" OR "bar syndrome" OR "ataxia telangiectasia"	1
" dock8" OR " dock 8" OR " dedicator of cytokinesis protein 8" OR " autosomal recessive hies" OR " ar-hies" OR "hyper immunoglobulin e" OR "hyper ige" OR "hyperimmunoglobulin e"	0
TOTAL BEFORE DEDUPLICATION	**31**
TOTAL AFTER DEDUPLICATION	**31**

ScanMedicine
https://scanmedicine.com/
Date searched: 8.5.24
Records found: 1

Limit: 2017+
Search: Devices

Search term	Results
"severe combined immuno deficiency" | "severe combined immunodeficiency" | SCID | "adenosine deaminase deficiency" | "ada deficiency"	1
"digeorge syndrome" | "di george syndrome" | "autosomal dominant opitz g bbb syndrome" | "22q11 deletion syndrome" | "22q11.2 deletion syndrome"	0
"louis bar disease" | "bar syndrome" | "ataxia telangiectasia"	0
" dock8" | " dock 8" | " dedicator of cytokinesis protein 8" | " autosomal recessive hies" | " ar-hies" | "hyper immunoglobulin e" | "hyper ige" | "hyperimmunoglobulin e"	0
TOTAL BEFORE DEDUPLICATION	**1**
TOTAL AFTER DEDUPLICATION	**1**

Orphanet
https://nbs.orphanet.app/
Date searched: 8.5.24
Records found: 4

Limit: 2017+

Search term	Results
Disease name: Severe combined immunodeficiency	1
Disease name: 22q11.2 deletion syndrome	1
Disease name: ataxia-telangiectasia	1
Disease name: Combined immunodeficiency due to DOCK8 deficiency	1
TOTAL BEFORE DEDUPLICATION	**4**
TOTAL AFTER DEDUPLICATION	**4**

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 5 of 12, May 2024
https://www.cochranelibrary.com/
Date searched: 8.5.24
Records found: 1

#1 MeSH descriptor: [22q11 Deletion Syndrome] explode all trees 19
#2 ("Di George" or DiGeorge) near/2 (syndrome* or anomal* or sequence*) 32
#3 "autosomal dominant opitz g bbb syndrome" 0
#4 "conotruncal anomaly face syndrome" 1
#5 ("pharyngeal pouch" or sedlackova or shprintzen or "velo cardio facial" or vcf or "thymic aplasia") NEAR/2 syndrome* 3
#6 "22q11 deletion syndrome" or "22q11.2 deletion syndrome" 18
#7 #1 or #2 or #3 or #4 or #5 or #6 with Cochrane Library publication date Between Jan 2017 and May 2024, in Cochrane Reviews 0
#8 MeSH descriptor: [Ataxia Telangiectasia] this term only 15
#9 ataxia near/2 (tel?angiectatica or tel?angiectasia) 96
#10 "Bar syndrome" or "Louis Bar disease" 1
#11 ("cerebello-oculocutaneous" or cerebellooculocutanea) near/2 (tel?angiectatica or tel?angiectasia) 0
#12 #8 or #9 or #10 or #11 with Cochrane Library publication date Between Jan 2017 and May 2024, in Cochrane Reviews 1
#13 "DOCK8" or "DOCK 8" 1
#14 "Dedicator of cytokinesis protein 8" 0
#15 "autosomal recessive HIES" or "AR-HIES" 0
#16 ("hyper immunoglobulin E" or "hyper IgE" or "hyperimmunoglobulin E") near/3 syndrome* 2
#17 #13 or #14 or #15 or #16 with Cochrane Library publication date Between Jan 2017 and May 2024, in Cochrane Reviews 0
#18 #7 or #12 or #17 1

International HTA Database
https://database.inahta.org/
Date searched: 8.5.24
Records found: 1

Limits: 2017+

18	**#17 OR #12 OR #7**	**3**
17	#16 OR #15 OR #14 OR #13	0
16	("hyper immunoglobulin E" or "hyper IgE" or "hyperimmunoglobulin E") and syndrome*	0
15	"autosomal recessive HIES" or "AR-HIES"	0
14	"Dedicator of cytokinesis protein 8"	0
13	"DOCK8" or "DOCK 8"	0
12	#11 OR #10 OR #9 OR #8	2
11	("cerebello-oculocutaneous" or cerebellooculocutanea) and (telangiectatica or telangiectasia)	0
10	"Bar syndrome" or "Louis Bar disease"	0
9	ataxia and (telangiectatica or telangiectasia)	2
8	"Ataxia Telangiectasia"[mhe]	1
7	#6 OR #5 OR #4 OR #3 OR #2 OR #1	1
6	"22q11* deletion syndrome"	0
5	("pharyngeal pouch" or sedlackova or shprintzen or "velo cardio facial" or vcf or "thymic aplasia") and syndrome*	0
4	"conotruncal anomaly face syndrome"	0
3	"autosomal dominant opitz g bbb syndrome"	0
2	("Di George" or DiGeorge) and (syndrome* or anomal* or sequence*)	1
1	"22q11 Deletion Syndrome"[mhe]	0

KSR Evidence
https://ksrevidence.com/
Date searched: 8.5.24
Records found: 43

1	("Di George" or DiGeorge) near/2 (syndrome* or anomal* or sequence*) in All text	10 results
2	"autosomal dominant opitz g bbb syndrome" in All text	0 results
3	"conotruncal anomaly face syndrome" in All text	0 results
4	("pharyngeal pouch" or sedlackova or shprintzen or "velo cardio facial" or vcf or "thymic aplasia") near/2 syndrome* in All text	1 result
5	"22q11* deletion syndrome" in All text	29 results
6	#1 or #2 or #3 or #4 or #5 in All text	33 results
7	ataxia near/2 (telangiectatica or telangiectasia) in All text	13 results
8	"Bar syndrome" or "Louis Bar disease" in All text	0 results
9	("cerebello-oculocutaneous" or cerebellooculocutanea) near/2 (telangiectatica or telangiectasia) in All text	0 results
10	#7 or #8 or #9 in All text	13 results
11	"DOCK8" or "DOCK 8" in All text	3 results
12	"Dedicator of cytokinesis protein 8" in All text	0 results
13	"autosomal recessive HIES" or "AR-HIES" in All text	0 results

14 ("hyper immunoglobulin E" or "hyper IgE" or "hyperimmunoglobulin E") near/3 syndrome* in All text 3 results
15 #11 or #12 or #13 or #14 in All text 5 results
16 #15 or #10 or #6 in All text 43 results
Filtered by: PUBLICATION DATE 2024, 2023, 2022, 2021, 2020, 2019, 2018, 2017

ClinicalTrials.gov
https://clinicaltrials.gov/
Date searched:
DiGeorge – 29.5.24
AT – 8.7.24
DOCK8 – 8.7.24
Records found:
DiGeorge – 18
AT - 31
DOCK8 - 21

Study start: 01/01/2017+

Search term	Results
"digeorge syndrome" OR "di george syndrome" OR "autosomal dominant opitz g bbb syndrome" OR "22q11 deletion syndrome" OR "22q11.2 deletion syndrome"	18
"louis bar disease" OR "bar syndrome" OR "ataxia telangiectasia"	31
" dock8" OR " dock 8" OR " dedicator of cytokinesis protein 8" OR " autosomal recessive hies" OR " ar-hies" OR "hyper immunoglobulin e" OR "hyper ige" OR "hyperimmunoglobulin e"	21
TOTAL BEFORE DEDUPLICATION	**70**
TOTAL AFTER DEDUPLICATION	**70**

International Clinical Trials Registry Platform (ICTRP)
https://trialsearch.who.int/AdvSearch.aspx
Date searched:
DiGeorge – 29.5.24
AT – 8.7.24
DOCK8 – 8.7.24
Records found:
DiGeorge – 10
AT - 22
DOCK8 - 3
Date of registration: 01/01/2017 to 29/05/2024 (DiGeorge)
01/01/2017 to 08/07/2024 (AT/DOCK8)
Recruitment status: ALL

Search term (Condition field; without synonyms)	Results
"digeorge syndrome" OR "di george syndrome" OR "autosomal dominant opitz g bbb syndrome" OR "22q11 deletion syndrome" OR "22q11.2 deletion syndrome"	10

"louis bar disease" OR "bar syndrome" OR "ataxia telangiectasia"	22
" dock8" OR " dock 8" OR " dedicator of cytokinesis protein 8" OR " autosomal recessive hies" OR " ar-hies" OR "hyper immunoglobulin e" OR "hyper ige" OR "hyperimmunoglobulin e"	3
TOTAL BEFORE DEDUPLICATION	**35**
TOTAL AFTER DEDUPLICATION	**35**

EU Clinical Trials Register
https://www.clinicaltrialsregister.eu/
Date searched:
DiGeorge – 29.5.24
AT – 8.7.24
DOCK8 – 8.7.24
Records found:
DiGeorge – 3
AT – 5
DOCK8 – 0
Date range: 2017-01-01 to 2024-05-29 (DiGeorge)
2017-01-01 to 2024-07-08 (AT/DOCK8)

Search term	Results
"digeorge syndrome" OR "di george syndrome" OR "autosomal dominant opitz g bbb syndrome" OR "22q11 deletion syndrome" OR "22q11.2 deletion syndrome"	3
"louis bar disease" OR "bar syndrome" OR "ataxia telangiectasia"	5
" dock8" OR " dock 8" OR " dedicator of cytokinesis protein 8" OR " autosomal recessive hies" OR " ar-hies" OR "hyper immunoglobulin e" OR "hyper ige" OR "hyperimmunoglobulin e"	0
TOTAL BEFORE DEDUPLICATION	**8**
TOTAL AFTER DEDUPLICATION	**8**

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. Twenty publications were ultimately judged to be relevant to one or more review questions and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

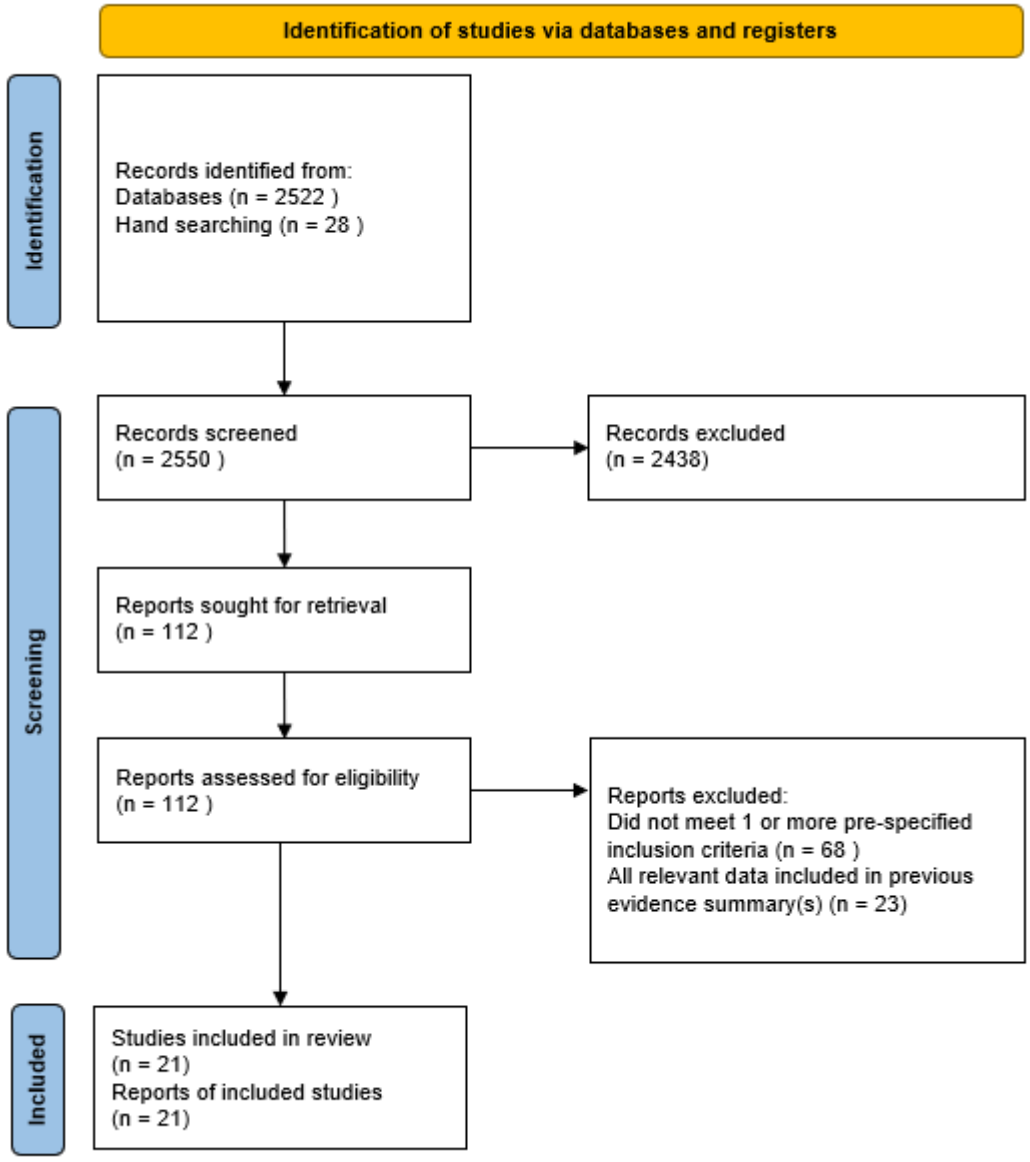


Figure 1: Summary of publications included and excluded at each stage of the review

Publications included after review of full-text articles

The 21 publications included after review of full-texts are summarised in Table 33 below.

The 23 publications which met the inclusion criteria for this evidence summary, but were not selected for data extraction and synthesis because all relevant data had already been included in either the most recent review conducted for the UK NSC,[4] the HIQA, Republic of Ireland report,[1] or both, are summarised in Table 34 below.

Table 33: Summary of publications included after review of full-text articles, and the question(s) each publication was identified as being relevant to

Study	The condition	The test	The intervention	The screening programme	Implementation criteria	Comments
Baekvad-Hansen, 2021[19]		✓				Criterion 4
Booth, 2022[20]		✓				Criterion 4
Boyarchuk, 2022[21]		✓				Criterion 4
Blom, 2021[11]				✓		Criterion 6
Blom, 2019[33]				✓		Criterion 6
Chan, 2021[22]		✓				Criterion 4
Heather, 2022[23]		✓				Criterion 4
Howley, 2024[36]				✓		Criterion 6
Kutsa, 2022[37]				✓		Criterion 6
Lev, 2022[24]		✓				Criterion 4
Liao, 2019[25]		✓				Criterion 4
Marakhonov, 2024[46]		✓				Criterion 4
Marinova, 2022[26]		✓				Criterion 4
Puck, 2021[27]		✓				Criterion 4
Speckmann, 2023[28]		✓				Criterion 4
Wakamatsu, 2022[29]		✓				Criterion 4
Raspa, 2024[35]				✓		Criterion 6
Schuetz, 2023[32]			✓			Criterion 9
Soomann, 2024[30]			✓			Criterion 9
Thakar, 2023[31]			✓			Criterion 9
Van Dijk, 2021[34]				✓		Criterion 6

Table 34: Summary of publications not selected for data extraction and synthesis (already included in previous reviews)

Study	The condition	The test	The intervention	The screening programme	Implementation criteria	Comments

Argudo-Ramirez, 2019[49]	✓		Criterion 4
Argudo-Ramirez, 2021[7]	✓		Criterion 4
Audrain, 2018[50]	✓		Criterion 4
Barbaro, 2017[51]	✓		Criterion 4
Blom, 2021[52]	✓		Criterion 4
Brown, 2011[63]		✓	Criterion 9
Chan, 2011[64]		✓	Criterion 9
Chien, 2015[62]	✓		Criterion 4
Cogley, 2021[53]	✓		Criterion 4
Gizewska, 2020[54]	✓		Criterion 4
Gongrich, 2021[8]	✓		Criterion 4
Hale, 2021[55]	✓		Criterion 4
Heimall, 2017[56]		✓	Criterion 9
Kwan, 2013[48]	✓		Criterion 4
Kwan, 2014[6]	✓		Criterion 4
Kwan, 2015[47]	✓		Criterion 4
Martin-Nalda, 2019[57]	✓		Criterion 4
Rechavi, 2017[9]	✓		Criterion 4
Strand, 2020[58]	✓		Criterion 4
Thomas, 2019[59]	✓		Criterion 4
Thorsen, 2021[13]	✓		Criterion 4
Verbsky, 2012[67]	✓		Criterion 4
Vogel, 2014[61]	✓		Criterion 4

Publications excluded after review of full text articles

Of the 112 publications assessed as potentially relevant after the review of titles and abstracts, 65 were ultimately judged not to be relevant to this review (did not meet the pre-specified inclusion criteria). These publications, along with reasons for exclusion, are listed in Table 35.

Table 35: Publications excluded after review of full text articles

Publication	Reason for exclusion (PICROS not met)
Abd Hamid, 2017[68]	Study reporting outcomes of HSCT in SCID patients only with no comparison by route of diagnosis (I, C, S)
Abd Hamid, 2018[69]	Study reporting outcomes of HSCT in SCID patients only with no comparison by route of diagnosis (I, C, S)
Adams, 2014[65]	TREC analysis of anonymised DBS from newborn screening with no confirmatory testing and TREC levels in known cases, no accuracy, incidence or screening outcomes data (R, O, S)

Albin-Leeds, 2017[70]	Outcomes of a cohort of non-SCID TREC positives with no identified cause of TCL (P, O, S)
Al-Mousa, 2018[71]	Retrospective TREC testing of DBS, suspected SCID reported but no confirmatory testing (no reference standard) (R, O, S)
Amatuni, 2019[72]	Conference abstract
Arnold, 2023 [73]	Not a primary study; discussion/review article
Atkins, 2021[74]	Study of relationship between TREC and gestational age (R, O, S)
Audrain, 2021[75]	Not a primary study; review article describing French NBS screening experience
Barreiros, 2022[76]	Targeted testing, not newborn screening (P, I, O, S)
Barzaghi, 2023[77]	Not a primary study; discussion/review article
Bayram, 2021[78]	Clinical characteristics and outcomes of patients with SCID (P, O, S)
Blom, 2017[79]	TREC analysis of anonymised DBS from newborn screening with no confirmatory testing and TREC levels in known cases, no accuracy, incidence or screening outcomes data (R, O, S)
Blom, 2018[80]	Not a primary study
Borte, 2012[81]	TREC analysis of anonymised DBS from NBS newborn screening with no confirmatory testing and TREC levels in known cases, no accuracy, incidence or screening outcomes data (R, O, S)
Buckley, 2011[82]	Long-term outcomes of HSCT, no comparison based on route of diagnosis (I, C, S)
Chase, 2011[83]	Not a primary study
Clement, 2015[84]	Cost-effectiveness analysis (France)
Demirtas, 2022[85]	Comparison of HSCT outcomes in SCID based on various characteristics, no data comparing routes of diagnosis (I, C)
Diamond, 2015[86]	Not a primary study; review article on diagnostic criteria
Dorsey, 2017[87]	Not a primary study; review of treatment of SCID
Dvorak, 2013[88]	Report of clinical characteristics of patients diagnosed with SCID in the US (P, I, C, O, S)
Dvorak, 2017[89]	Conference abstract
Dvorak, 2023[90]	Report of diagnostic criteria for SCID (P, C, O, S)
Dvorak, 2023[91]	Report of the development process for diagnostic criteria for SCID (P, C, O, S)
Elliman, 2022[92]	Conference abstract
Gans, 2020[93]	Characteristics of screen positive patients only, no accuracy or incidence data (P, O)
Gaviglio, 2023[94]	Retrospective analysis of TREC levels by gestational age, determination of thresholds for pre-term babies, no accuracy data or screening outcomes (O, S)
Gennery, 2018[95]	Not a primary study; comment on journal article
Hardin, 2022[96]	HSCT outcomes for transplantation before versus after 3.5 months, method of SCID detection not reported (I, C)
Howley, 2024[97]	Not SCID; report of outcomes for NBS screening versus later identification of athymic infants, including 22q11.2 DS (P)
Ikinciogullari, 2019[98]	Report of outcomes of SCID patients, not screening related (I, C, R, S)
Kanegae, 2016[99]	TREC analysis of DBS from newborn screening with no confirmatory testing and TREC levels in known cases, no accuracy or incidence data (R, O, S)
Kanegae, 2017[100]	Assay validation study, includes newborns and older positive control patients (P, O, S)
Krantz, 2019[101]	Case series (I, C, R, O, S)
Kubala, 2022[102]	Natural history of non-SCID TREC positives identified through screening, no accuracy of incidence data (P, R, O, S)
Kuo, 2020[103]	*ADA* SCID registry (I, C, S)
Lankester, 2022[104]	Multivariable regression analysis of factors affecting survival of patients with SCID post-HSCT, no screening or early diagnosis variable assessed (I, C)

Mahase, 2019[105]	Not a primary study, news article on gene therapy
Mantravadi, 2021[106]	Diagnosis and clinical outcomes of TREC screen positive patients, no accuracy of incidence data (P, R, O, S)
Miyamoto, 2021[107]	Multivariable regression analysis of factors affecting survival of patients with SCID post-HSCT, no screening or early diagnosis variable assessed (I, C)
Nightingale, 2021[108]	Not a primary study, news article on Public Health England pilot
Nourizadeh, 2018[109]	Threshold finding study, no accuracy of incidence data (O)
Pai, 2014[110]	Outcomes of HSCT in SCID patients only, no comparison by route of diagnosis (I, C)
Raspa, 2020[111]	Needs of families with an infant diagnosed with SCID through screening, no acceptability outcomes (O)
Reid, 2017[112]	Conference abstract
Reinhardt, 2021[113]	Outcomes of patients with *ADA* SCID treated with gene therapy, no route of diagnosis comparison (I, C, S)
Remaschi, 2021[114]	Evaluation of TREC and KREC levels in newborns and factors affecting these (R, O, S)
Richards, 2018[115]	Retrospective TREC testing of DBS from known SCID and 22q11.2 DS cases (P, R, O, S)
Richards, 2020[116]	Not a primary study, Australia/New Zealand practice guideline on diagnosis and management of SCID
Roifman, 2023[117]	Not a primary study; report of an up-date to Canadian screening algorithms
Rozmus, 2013[118]	Report of clinical characteristics of patients diagnosed with SCID (I, C, R, O, S)
Schoenaker, 2020[119]	Diagnostic preferences of parents of infants with A-T (P, I, O, S)
Shearer, 2014[120]	Article on establishing diagnostic criteria for SCID (I, C, R, O, S)
Smith, 2021[121]	Patient/parent perspectives on treatment for SCID, not screening (P, I)
Son, 2017[122]	Threshold finding study, Korea (R, S)
South, 2019[123]	Not a primary study, publication of EAG report on gene therapy HST (Strimvelis for *ADA* SCID)
Tagliaferri, 2017[124]	TREC analysis of anonymised DBS from newborn screening with no confirmatory testing and TREC levels in known cases, no accuracy or incidence data (R, O, S)
Tang, 2023[125]	Non-English language publication
Thomas, 2015[126]	Non-English language publication
Thompson, 2018[127]	Assay development study (P, R, O, S)
Truck, 2020[128]	Not a primary study, review article about NBS screening for SCID in Switzerland
van den Akker-Van Marle, 2021[129]	Netherlands cost-effectiveness study (O, S)
Van der Ploeg, 2019[130]	Cost-effectiveness modelling study (O, S)
Verbsky, 2012[67]	Not a primary study, review article
Vidal-Folch, 2017[131]	Diagnostic case-control study evaluating new PCR method for TREC, 'control group' only used to establish reference range, clinical accuracy data incomplete (O)
Erratum, 2104[132]	Not a primary study, Erratum, correction to author contribution only
News article, 2023[133]	Not a primary study, news article

ADA: adenosine deaminase deficient; A-T: ataxia telangiectasia; C: comparator; DBS: dried blood spot; DS: deletion syndrome; EAG: External Assessment Group; I: intervention or index test; HSCT: hematopoietic stem cell transplant; HST: Highly Specialised Technology; KREC: K-deleting recombination excision circle; NBS: newborn blood spot; O: outcomes; P: population; PCR: polymerase chain reaction; S: study design; SCID: severe combined immunodeficiency; TCL: T-cell lymphopenia; TREC: T-cell receptor excision circle

Appendix 3 — Summary and appraisal of individual studies

Data Extraction

Table 36 provides a study-level summary of all accuracy and partial accuracy data extracted.

Table 36: Study level summary of accuracy data relevant to criterion 4

Study	N	Target condition	TP	FP	TN	FN	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Baekvad-Hansen, 2021[19]	53,221	SCID non-SCID TCL classified as FP	0	1	NR	NR	NE	NE	NE	NE
Boyarchuck, 2022[21]	10,350	SCID non-SCID TCL classified as FP	1	2	NR	NR	NE	NE	NE	NE
Booth, 2022[20]	159,730	TCL SCID and non-SCID TCL classified as TP	22	5	159,703	0	100 (84.56, 100)	100 (99.99, 100)	81.48 (64.68, 91.36)	100 (100, 100)
		SCID non-SCID TCL classified as FP	7	20	159,703	0	100 (59.04, 100)	99.99 (99.98, 99.99)	25.93 (18.42, 35.17)	100 (100, 100)
Chan, 2021[22]	35,888	SCID non-SCID TCL classified as FP	0	13	NR	NR	NE	NE	NE	NE
Heather, 2022[23]	191,075	SCID non-SCID TCL classified as FP	2	50	191,023	0	100 (15.81, 100)	99.97 (99.97, 99.98)	3.85 (2.94, 5.01)	100 (100, 100)

		TCL SCID and non-SCID TCL classified as TP	23	29	191,023	0	100 (85.18, 100)	99.98 (99.98, 99.99)	44.23 (35.53, 53.30)	100 (100, 100)
Lev, 2022[24]	937,953	SCID non-SCID TCL classified as FP	30	112	937,811	0	100 (88.43, 100)	99.99 (99.99, 99.99)	21.13 (18.21, 24.38)	100 (100, 100)
		SCID and 22q11.2 DS other non-SCID TCL classified as FP	32	110	937,811	0	100 (89.11, 100)	99.99 (99.99, 99.99)	22.54 (19.44, 25.96)	100 (100, 100)
		TCL SCID and non-SCID TCL classified as TP	105	37	937,811	0	100 (96.55, 100)	100 (99.99, 100)	73.94 (67.28, 79.66)	100 (100, 100)
Liao, 2019[25]	253,999	SCID non-SCID TCL classified as FP	2	54	NR	NR	NE	NE	3.57 (2.76, 4.61)	NE
Puck, 2021[27]	3,252,156	SCID non-SCID TCL classified as FP	50	512	3,251,592	2	96.15 (86.79, 99.53)	99.98 (99.98, 99.99)	8.90 (8.10, 9.76)	100 (100, 100)

		TCL SCID and non-SCID TCL classified as TP	212	350	NR	NR	NE	NE	37.72 (35.28, 40.23)	NE
Speckmann, 2023[28]	1,878,985	SCID	35	146	NR	NR	NE	NE	19.33 (16.93, 21.99)	NE
		non-SCID TCL classified as FP								
		TCL	115	66	NR	NR	NE	NE	34.64 (29.40, 40.29)	NE
		SCID and non-SCID TCL classified as TP								
		primary TCL	84	97	NR	NR	NE	NE	26.51 (22.82, 30.56)	NE
		SCID and non-SCID TCL classified as TP, secondary TCL classified as FP								
Wakamatsu, 2022[29]	137,484	SCID	2	128	NR	NR	NE	NE	1.54 (1.30, 1.82)	NE
		non-SCID TCL classified as FP								
		TCL	78	52	NR	NR	NE	NE	60.0 (53.34, 66.31)	NE

	SCID and non-SCID TCL classified as TP

CI: confidence interval; DS: deletion syndrome; FN: false negative; FP: false positive; N: number in study; NE: not estimable; NR: not reported; NPV: negative predictive value; PPV: positive predictive value; SCID: severe immunodeficiency; TCL: T-cell lymphopenia; TN: true negative; TP: true positive

Appraisal for quality and risk of bias

QUADAS-2 assessments

STUDY: Booth, 2022 [20]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Retrospective chart review of the first 2 years of NBS screening for SCID in Arizona, US. The analysed cohort appears to have included all births in Arizona during the study period.

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes

Could the selection of patients have introduced bias? **RISK: Low**

B. APPLICABILITY

All babies born in Arizona during the study period appear to have been included.

Do the included patients match the question? **Concerns: Low**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

TREC analysis in DBS samples, with repeat testing of positive samples and repeat sampling at term-adjusted gestational age for premature newborns with an initial abnormal result (pre-specified cut-off). Screen positive patients were referred for specialist immunological evaluation and genetic testing.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes

Could the conduct or interpretation of the index test have introduced bias? **RISK: Low**

B. APPLICABILITY

RT-PCR analysis of TREC in DBS samples, using a commercial kit.

Are there concerns that the index test, its conduct, or interpretation differ from the review question? **Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

Screen positive patients were referred for specialist immunological evaluation and genetic testing. The article states that there were no FN tests that the Arizona department of Health Services or the Phoenix Children's Hospital were aware of, but it is unclear how this was established.

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: High**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

Screen negative babies did not receive further follow up and it is not clear how the study authors determined that no cases of SCID were missed during the study period.

Was there an appropriate time interval between index test and reference standard?	No
Did patients receive the same or a similar reference standard?	No
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: High**

STUDY: Heather, 2022[23]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Retrospective review of the first 3 years of NBS screening for SCID in New Zealand. All babies screened for SCID in New Zealand during the study period were included.

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes

Could the selection of patients have introduced bias? **RISK: Low**

B. APPLICABILITY

All babies screened for SCID in New Zealand during the study period were included.

Do the included patients match the question? **Concerns: Low**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

TREC analysis in DBS samples, with a repeat sample tested at 2 weeks for babies born ≤1,500 g and a further repeat sample tested at 1 month for babies born ≤1,000 g. Different, pre-specified test thresholds were used to define screen positive and urgent screen positive.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes

Could the conduct or interpretation of the index test have introduced bias? **RISK: Low**

B. APPLICABILITY

RT-PCR analysis of TREC in DBS samples, using a commercial kit.

Are there concerns that the index test, its conduct, or interpretation differ from the review question? **Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

No details were reported about the follow-up investigations used to confirm diagnosis in screen positive babies. The article states that, to date, no cases of SCID have been diagnosed that were not detected by the screening programme, but it is not clear how this was established.

Is the reference standard likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index test?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: High**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

No details of the follow-up investigation of screen positive babies were reported. Screen negative babies did not receive further follow-up and it is not clear how the study authors determined that no cases of SCID were missed during the study period.

Was there an appropriate time interval between index test and reference standard?	No
Did patients receive the same or a similar reference standard?	No
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: High**

STUDY: Lev, 2022[24]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Retrospective records analysis of all babies screened in the first 5 years of NBS screening for SCID in Israel.

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes

Could the selection of patients have introduced bias? **RISK: Low**

B. APPLICABILITY

All babies born in Israel during the study period were included.

Do the included patients match the question? **Concerns: Low**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

TREC analysis in DBS samples, with repeat testing of positive samples and repeat sampling where both initial tests were positive (pre-specified cut-off). Screen positive patients were referred for specialist immunological evaluation and genetic testing.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes

Could the conduct or interpretation of the index test have introduced bias? **RISK: Low**

B. APPLICABILITY

RT-PCR analysis of TREC in DBS samples, using a commercial kit.

Are there concerns that the index test, its conduct, or interpretation differ from the review question? **Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

Screen positive patients were referred for specialist immunological evaluation and genetic testing. The article states that no cases of SCID were missed during the study period, but it is unclear how this was established.

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: High**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

Screen negative babies did not receive further follow-up and it is not clear how the study authors determined that no cases of SCID were missed during the study period.

Was there an appropriate time interval between index test and reference standard?	No
Did patients receive the same or a similar reference standard?	No
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: High**

STUDY: Liao, 2019[25]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Retrospective report of experience of NBS screening for SCID in Taiwan, and re-analysis of DBS sample from newborns with TREC results <90 copies/μL.

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes

Could the selection of patients have introduced bias? **RISK: Low**

B. APPLICABILITY

All newborns enrolled in the SCID screening programme during the study period, and 486 newborns with a TREC screening result <90 copies/μL

Do the included patients match the question? **Concerns: Low**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

TREC analysis in DBS with repeat testing of positives and repeat sampling for positive premature or low birth weight newborns. Repeat analysis of DBS with TREC results <90 copies/μL for 22q11.2 DS evaluation.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes

Could the conduct or interpretation of the index test have introduced bias? **RISK: Low**

B. APPLICABILITY

RT-PCR analysis of TREC in DBS samples.

Are there concerns that the index test, its conduct, or interpretation differ from the review question? **Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

Complete blood count and flow cytometry, screen positives only, no details reported of any missed cases. Genetic testing of all samples in the 22q11.2 DS evaluation (qRT-PCR was used to detect the copy number of TBX1 and HIRA

genes by simple DNA extraction method. Multiplex ligation dependent probe amplification was used for further confirmation).

Is the reference standard likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index test?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: High**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

Screen negative babies did not receive further follow-up and it is not clear how the study authors determined whether any cases of SCID were missed during the study period. Non-SCID TCL (other than 22q11.2 DS) were not reported.

Was there an appropriate time interval between index test and reference standard?	No
Did patients receive the same or a similar reference standard?	No
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: High**

STUDY: Puck 2021[27]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Retrospective report of first 6.5 years' experience of NBS screening for SCID in California.

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes

Could the selection of patients have introduced bias? **RISK: Low**

B. APPLICABILITY

All babies screened for SCID in California during the first 6.5 years after introduction.

Do the included patients match the question? **Concerns: Low**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

TREC analysis in DBS with repeat testing/sampling of positives (pre-specified cut-off) and referral of screen positives for flow cytometry followed by further specialist investigations where appropriate.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes

Could the conduct or interpretation of the index test have introduced bias? **RISK: Low**

B. APPLICABILITY

RT-PCR analysis of TREC in DBS samples, using a commercial kit.

Are there concerns that the index test, its conduct, or interpretation differ from the review question? **Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

Screen positives referred for flow cytometry followed by further specialist investigations where appropriate. The article states that two screen negative babies were subsequently diagnosed with late SCID following repeat infections.

Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: High**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

Screen negative babies did not receive further follow-up and it is not clear how the study authors determined that no further cases of SCID were missed during the study period.

Was there an appropriate time interval between index test and reference standard?	No
Did patients receive the same or a similar reference standard?	No
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: High**

STUDY: Speckmann, 2023[28]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Retrospective report of first 3 years' experience of NBS screening for SCID in Germany.

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes

Could the selection of patients have introduced bias? **RISK: Low**

B. APPLICABILITY

All babies with documented TREC NBS screening during the study period.

Do the included patients match the question? **Concerns: Low**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

TREC analysis in DBS (pre-specified cut-off) with repeat sampling of positives and referral of screen positives for flow cytometry followed by further specialist investigations where appropriate.

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes

Could the conduct or interpretation of the index test have introduced bias? **RISK: Low**

B. APPLICABILITY

RT-PCR analysis of TREC in DBS samples, using a commercial kit.

Are there concerns that the index test, its conduct, or interpretation differ from the review question? **Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

Two stages of confirmatory/follow-up testing, no follow-up of screen negatives, and no details reported of any missed cases.

Is the reference standard likely to correctly classify the target condition?	Yes

Were the reference standard results interpreted without knowledge of the results of the index test?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: High**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

Screen negative babies did not receive further follow-up and it is not clear how the study authors determined whether any cases of SCID were missed during the study period. Some loss to follow-up was reported, but not all screened infants were accounted for in the study flow chart.

Was there an appropriate time interval between index test and reference standard?	No
Did patients receive the same or a similar reference standard?	No
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

STUDY: Wakamatsu, 2022[29]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS

Retrospective report of first 5 years' experience of NBS screening for SCID in Japan.

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes

Could the selection of patients have introduced bias? **RISK: Low**

B. APPLICABILITY

All babies screened for SCID in Japan during the first 5 years after introduction.

Do the included patients match the question? **Concerns: Low**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS

TREC analysis of DBS, with repeat on new DBS for positives (pre-specified cut-off)

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes

Could the conduct or interpretation of the index test have introduced bias? **RISK: Low**

B. APPLICABILITY

RT-PCR analysis of TREC in DBS samples, using a commercial kit.

Are there concerns that the index test, its conduct, or interpretation differ from the review question? **Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS

Screen positive patients were referred for specialist immunological evaluation and genetic testing. No follow-up of screen negatives, and no details reported of any missed cases.

Is the reference standard likely to correctly classify the target condition?	Yes

Were the reference standard results interpreted without knowledge of the results of the index test?	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: High**

B. APPLICABILITY

Is there concern that the target condition as defined by the reference standard does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS

Screen negative babies did not receive further follow-up and it is not clear how the study authors determined whether any cases of SCID were missed during the study period.

Was there an appropriate time interval between index test and reference standard?	No
Did patients receive the same or a similar reference standard?	No
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: High**

QUIPS assessments

STUDY: Schuetz, 2023[32]

Study participation	
Adequate participation in study by eligible persons?	Yes
Description of the source population or population of interest?	Yes
Description of baseline study sample?	Yes
Adequate description of the sampling frame and recruitment?	Yes
Adequate description of the period and place of recruitment?	Yes
Adequate description of inclusion and exclusion criteria?	Yes
Risk of bias	**Low**

Study attrition	
Adequate response rate for study participants?	NA
Description of attempts to collect information on participants who dropped out?	NA
Reasons for loss to follow-up provided?	NA
Adequate description of participants lost to follow-up?	NA
No important differences between participants who completed the study and those who did not?	NA
Risk of bias	**NA**

Prognostic factor measurement	
Clear definition or description of the prognostic factor provided?	Yes
Method of prognostic factor measurement is adequately valid and reliable?	Yes
Continuous variables are reported or appropriate cut points are used?	Yes
The method and setting of prognostic factor measurement is the same for all participants?	Yes
Adequate proportion of the study sample has complete data for prognostic factor?	Yes
Appropriate methods of imputation are used for missing prognostic factor data?	NA
Risk of bias	**Low**

Outcome measurement	
A clear definition of the outcome is provided?	Yes
Method of outcome measurement used is adequately valid and reliable?	Yes
Method and setting of outcome measurement is the same for all study participants?	Yes
Risk of bias	**Low**

Study confounding	
All of the important confounders are measured?	Yes
Clear definitions of the important confounders measured are provided?	Yes
Measurement of all important confounders is adequately valid and reliable?	Yes

The method and setting of confounder measurement are the same for all study participants?	Yes
Appropriate methods are used if imputation is used for missing confounder data?	NA
Important potential confounders are accounted for in the study design?	Yes
Important potential confounders are accounted for in the analysis?	Yes
Risk of bias	**Low**

Statistical analysis and reporting	
Sufficient presentation of data to assess the adequacy of the analytical strategy?	Yes
Strategy for model building is appropriate and is based on a conceptual framework or model?	Yes
The selected statistical model is adequate for the design of the study?	Yes
There is no selective reporting of results?	Yes
Risk of bias	**Low**

STUDY: Thakar, 2023[31]

Study participation	
Adequate participation in study by eligible persons?	Yes
Description of the source population or population of interest?	Yes
Description of baseline study sample?	Yes
Adequate description of the sampling frame and recruitment?	Yes
Adequate description of the period and place of recruitment?	Yes
Adequate description of inclusion and exclusion criteria?	Yes
Risk of bias	**Low**

Study attrition	
Adequate response rate for study participants?	NA
Description of attempts to collect information on participants who dropped out?	NA
Reasons for loss to follow-up provided?	NA
Adequate description of participants lost to follow-up?	NA
No important differences between participants who completed the study and those who did not?	NA
Risk of bias	**NA**

Prognostic factor measurement	
Clear definition or description of the prognostic factor provided?	Yes
Method of prognostic factor measurement is adequately valid and reliable?	Yes
Continuous variables are reported or appropriate cut points are used?	Yes
The method and setting of prognostic factor measurement is the same for all participants?	Yes
Adequate proportion of the study sample has complete data for prognostic factor?	Yes
Appropriate methods of imputation are used for missing prognostic factor data?	NA
Risk of bias	**Low**

Outcome measurement	
A clear definition of the outcome is provided?	Yes
Method of outcome measurement used is adequately valid and reliable?	Yes
Method and setting of outcome measurement is the same for all study participants?	Yes
Risk of bias	**Low**

Study confounding	
All-important confounders are measured?	Yes
Clear definitions of the important confounders measured are provided?	Yes
Measurement of all important confounders is adequately valid and reliable?	Yes
The method and setting of confounder measurement are the same for all study participants?	Yes

Appropriate methods are used if imputation is used for missing confounder data?	NA
Important potential confounders are accounted for in the study design?	Yes
Important potential confounders are accounted for in the analysis?	Yes
Risk of bias	**Low**

Statistical analysis and reporting	
Sufficient presentation of data to assess the adequacy of the analytical strategy?	Yes
Strategy for model building is appropriate and is based on a conceptual framework or model?	Yes
The selected statistical model is adequate for the design of the study?	Yes
There is no selective reporting of results?	Yes
Risk of bias	**Low**

Table 37: Adapted CASP checklist summary for cohort studies of treatment, as used in Leaviss at al. 2017[4]

Study	Clearly focused question?	Acceptable cohort recruitment?	Exposure accurately measured?	Outcome accurately measured?	Identification of confounders?	Confounders taken into account?	Follow-up complete?	Follow-up long enough?	How precise are the results?	Results fit with other studies?
Soomann, 2024[30]	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	No	Yes

Table 38: MMAT assessments for acceptability (question 3) studies

Study	Screening questions		Qualitative					Mixed-methods				
	S1	S2	1.1	1.2	1.3	1.4	1.5	4.1	4.2	4.3	4.4	4.5
Blom, 2021[11]	Y	Y						Y	Y	CT	Y	Y
Blom, 2019[33]	Y	Y						Y	Y	CT	Y	Y
Howley, 2024[36]	Y	CT	CT	CT	Y	Y	CT					
Kutsa, 2022[37]	Y	Y	Y	Y	Y	Y	Y					
Raspa, 2024[35]	Y	Y	Y	Y	Y	Y	Y					
van Dijk, 2021[34]	Y	Y	Y	Y	Y	Y	Y					

CT: cannot tell; Y: yes

S1: Are there clear research questions?
S2: Do the collected data allow to address the research questions?

1.1: Is the qualitative approach appropriate to answer the research question?
1.2: Are the qualitative data collection methods adequate to address the research question?
1.3: Are the findings adequately derived from the data?
1.4: Is the interpretation of results sufficiently substantiated by data?
1.5: Is there coherence between qualitative data sources, collection, analysis and interpretation?

4.1: Is there an adequate rationale for using a mixed methods design to address the research question?
4.2: Are the different components of the study effectively integrated to answer the research question?
4.3: Are the outputs of the integration of qualitative and quantitative components adequately interpreted?
4.4: Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?
4.5: Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?

Appendix 4 – Non-SCID causes of abnormal TREC screening results

As described in the background section of this report, there are a number of non-SCID, congenital conditions that can result in an abnormal TREC result at screening; there is no population screening programme that targets these conditions. Given the number and prevalence of differential diagnoses that may be identified as a result of TREC screening, the potential consequences of these additional diagnoses (e.g. further diagnostic testing, potential for treatment/management, potential for improved outcomes with earlier intervention) is likely to be of interest to decision makers when considering the introduction of TREC-based screening for SCID.

This Appendix comprises a series of vignettes of some of the non-SCID congenital conditions that can be identified by TREC-based screening. The current state of knowledge in respect of the aetiology, epidemiology, diagnosis and management of these conditions is summarised.

22q11.2 Deletion Syndrome

Clinical characteristics

22q11.2 deletion syndrome (22q11.2 DS) includes a number of phenotypes, previously described as: DiGeorge syndrome; velocardiofacial syndrome; conotruncal anomaly face syndrome; autosomal dominant Opitz G/BBB syndrome; Sedlackova syndrome; Cayler cardiofacial syndrome.[134]

Reduced gene expression on 22q11.2 is responsible for a wide range of clinical findings in 22q11.2 DS, including: congenital heart disease; particularly conotruncal malformations (ventricular septal defect, tetralogy of Fallot, interrupted aortic arch, and truncus arteriosus); palatal abnormalities (velopharyngeal incompetence, submucosal cleft palate, bifiduvula, and cleft palate); immune deficiency; characteristic facial features; learning difficulties; hearing loss. Laryngotracheoesophageal, gastrointestinal, ophthalmologic, central nervous system, skeletal, and genitourinary anomalies may also occur, and psychiatric illness and autoimmune disorders are more common in individuals with 22q11.2 DS.[134] Data from a large longitudinal cohort (n=1,412), diagnosed between 1992 and 2018 at a specialist centre (the 22q and You Center, Children's University hospital of Philadelphia) provides an indication of the proportion of 22q11.2 DS patients with various clinical presentations/comorbidities: Immune dysfunction (T-cell dysfunction 50%, humoral dysfunction 17%); cardiac 64%; craniofacial (velopharyngeal dysfunction 52%, submucous cleft palate 21%, overt cleft palate 6%); gastrointestinal (constipation 35%, dysphagia 30%, tube feeding 21%, G tube placement 16%); hypocalcaemia 55%; musculoskeletal; (scoliosis 50%, cervical spine abnormalities 46%); genitourinary (renal anomalies 16%, cryptorchidism 4%, hypospadias 4%); neurological/psychiatric (attention deficit hyperactivity disorder 52%, autism spectrum disorder 19%, seizures 15%, psychotic disorder 15%); malignancy 6%.[135] The median age at diagnosis, in the '22q and You' cohort, was 360 days; median age at diagnosis was substantially higher (3.1 years) in individuals without cardiac issues than in those with cardiac issues (2.6 months).[135]

Incidence and prevalence

The heterogeneity in clinical presentation and symptom severity, as well as a lack of universal screening, internationally, has resulted in uncertainty around the prevalence of 22q11.2 DS. A population-based study, conducted in Western Sweden, reported a mean annual incidence (over the 10 year period from 1991 to 2000) of 1.4 (95% CI: 9.1 to 20.8) per 100,000 live births.[136] The prevalence of 22q11.2 DS, in children younger than 16 years on 31 December 2000, was 1 in 7,577.[136] A US study, evaluating data on infants who were born from 1994 through 1999 to women residing in metropolitan Atlanta, reported a 22q11.2 DS prevalence of 1 in 5,950 (95% CI: 1 in 4417 to 1 in 8224) births.[137] Whilst a more recent cross-sectional study, based on analysis of a sample of 30,074 DBS collected by Newborn Screening Ontario between January 2017 and September 2018, estimated the minimum live-birth prevalence to be considerably higher at 1 in 2,148 (4.7 per 10,000, 95% CI: 2.5 to 7.8 per 10,000).[138] Of the 14 individuals with 22q11.2 DS identified from the Ontario sample, 6 (46%) had a TREC value below the initial newborn screening cut-off value for SCID (100 copies/3 µL), however, only 1 individual had a TREC value below the second confirmatory threshold (75 copies/3 µL).[138]

Detection through newborn screening

Data from the Ontario study indicates that an uncertain proportion of children with 22q11.2 DS may be detected through newborn screening for SCID.[138] The early identification of these children may facilitate comprehensive assessment within the first year of life, as recommended in the 22q11.2 Society guidelines,[139] and timely management (e.g. avoidance of live vaccines, calcium supplementation and avoidance of neonatal hypercalcaemic seizures, early thymus transplant in cases of severe T-cell deficiency). Identification through TREC-based screening provides the early immunological assessment recommended by the Clinical Immunology Society.[140] Patients with athymia or a severe T-cell deficiency will have an abnormal TREC result; congenital athymia is characterised by the lack of a functional thymus and most infants with congenital athymia have chromosome 22q11.2 DS, or CHARGE syndrome. A recent UK study compared age at referral and complications between athymic infants diagnosed following clinical presentation (n=25) and those diagnosed through NBS screening (n=19), who were referred for thymus transplantation at GOSH, London, UK.[97] This study included 17 patients with 22q11.2 DS, of whom 8 were identified through NBS screening.[97] Although this was a small study, the results provide some information about the effects of early (NBS screening) identification of athymic individuals on time to treatment and subsequent outcomes: the proportion of infants with invasive infections at the time of referral was lower in the NBS screening group, 3/19 (16%), than in the non-NBS screening group, 12/25 (48%); 6 patients, all of whom were in the non-NBS screening group died of systemic viral infections before treatment; a higher proportion of patients in the NBS screening group, 6/15 (40%) than in the non-NBS screening group, 2/11 (18%), received transplantation before the age of 4 months and treatment before 4 months was associated with higher thymic output at 6 and 12 months post-transplantation; all 3 post-transplant deaths occurred in patients in the non-NBS screening group.[97] It is important to note however, that only those neonates with significant to severe TCL would be identified by TREC-based NBS screening; those with no or mild T-cell deficiency would be expected to have a normal TREC result and some neonates with significant T-cell deficiency may also have a normal result.[140]

The current systematic review included 9 retrospective reports of experience from implemented TREC-based NBS screening programmes for SCID,[19, 20, 22-25, 27-29] of

which 7 reported details of non-SCID TCL screening outcomes.[20, 22-24, 27-29] All of these studies reported that screening for SCID had identified at least 1 case of 22q11.2 DS. The proportions of screen-positive results which led to a diagnosis of 22q11.2 DS varied widely and were as follows: 2/22 (9.09%), Arizona, US[20]; 1/13 (7.69%), Singapore[22]; 8/21 (38.1%), New Zealand[23]; 12/105 (11.3%), Israel[24]; 46/212 (21.7%), California, US[27]; 17/115 (14.78%), Germany[28]; 5/78 (6.41%), and Japan.[29]

Establishing a diagnosis – genetic testing

Most individuals with 22q11.2 DS (approximately 85%) affected individuals have a 2.54 Mb deletion, encompassing approximately 40 genes, with the remainder having smaller, atypical or 'nested' deletions. The deletion is *de novo* in >90% of affected individuals and inherited from a heterozygous parent in about 10%. Where it is inherited, 22q11.2 DS is an autosomal dominant contiguous gene DS. Most individuals with a 22q11.2 recurrent deletion (defined as a deletion of a specific size, usually mediated by nonallelic homologous recombination, occurring multiple times in the general population) are identified by chromosomal microarray analysis (CMA), using oligonucleotide arrays or single nucleotide polymorphism (SNP) arrays, performed due to observed clinical symptoms. Targeted genetic testing of at risk family members (asymptomatic siblings and parents of an affected individual) may be considered appropriate in order to identify, as early as possible, individuals who could benefit from cardiac and immunologic evaluation and evaluations and surveillance for other complications of 22q11.2 DS. Targeted deletion analysis methods, including fluorescence in-situ hybridisation (FISH), quantitative polymerase chain reaction (qPCR) and multiplex ligation-dependent probe amplification (MLPA) can be used to test at risk relatives of a person with a known 22q11.2 recurrent deletion, but are not used where a recurrent deletion has not previously been detected by CMA; some atypical deletions are not identifiable using current commercially available FISH probes.[134]

Clinical guidelines

The 22q11.2 Society, a UK-registered charity promoting 'both basic science and clinical interdisciplinary research into the biology of the 22q11.2 region, and the diagnosis, prognosis, and management of related disorders,' published its up-dated clinical practice guidelines for the management of children with 22q11.2 DS in 2023.[139] The 22q11.2 Society guidelines provide comprehensive recommendations for the assessment, monitoring and management of children and adolescents (0 to 18 years) with 22q11.2 DS and include recommendations for a substantial number of assessments in the first year of life.[139] These recommended investigations encompass a wide variety of specialities, including cardiology, immunology, endocrinology, ophthalmology, audiology, and speech and language development.[139] Parental testing is recommended to determine whether the 22q11.2 deletion is de novo or inherited from a parent and, where inherited, to provide care and genetic counselling (including reproductive counselling) for the affected parent.[139] With respect to specific interventions, the guideline notes that immune status should be checked before vaccination and live vaccines should not be given if T-cells are very low (CD4 <400 or naive CD4 <100 cells/mm3) and that vitamin D should be recommended to reduce the risk of hypocalcaemia.[139]

The, USA-based, Clinical Immunology Society has recently published clinical practice guidelines specific to the immunological management of patients with defects of thymic development, including 22q11.2 DS.[140] This guideline notes that the presence

or absence of immune deficiency cannot be assessed based on the clinical phenotype of 22q11.2 DS and states that immunological assessment is necessary to characterise immune status and assess infection susceptibility.[140] The most important requirement of initial assessment is stated to be *'rule-out of congenital athymia'*; patients with congenital athymia require immediate isolation precautions and eventual thymic transplant, and failure to diagnose this condition early in life can result in fatal infections.[140] Immunological assessment can also inform the safety of live vaccinations, infection susceptibility, the need for prophylactic antibiotics including to prevent pneumonias related to severe T-cell deficiencies.[140]

Horizon scanning for new treatment options

We have searched clinical trials registries (ClinicalTrials.gov, EUCTR and ICTRP) for 22q11.2 DS, from 2017 to present, with the aim of identifying any un-published or ongoing studies of novel treatments for 22q11.2 DS for which early identification may be clinically relevant. Our searches retrieved a total of 31 entries, of which 14 related to trials of treatment. All treatment trials were conducted in older children or adults and 12/14 concerned interventions to manage symptoms related to psychological or developmental disorders; no trials of disease-modifying interventions were identified.

Ataxia-telangiectasia

Clinical characteristics

Ataxia telangiectasia (A-T) is a rare genetic condition that affects the immunological, neurological, and other systems of the body. It is also known as ‘ataxia-telangiectasia syndrome’ or ‘Louis-Bar syndrome’. It is a complex, multisystem disorder, with substantial inter-individual variation in the severity of features.[141, 142] A-T is often described has having a "classic A-T" phenotype and a "variant A-T" phenotype. In practice, these categories describe a continuum of disease severity with "classic A-T" being used to describe the sever end of the phenotypic spectrum and "variant A-T" describing milder disease.[142]

Neurologic features

“Classic A-T” most commonly presents as cerebellar ataxia, observed as a child starts to sit and walk.[142, 143] Children with “classic A-T” exhibit multiple, progressive neurologic manifestations (initially cerebellar ataxia, followed typically by extrapyramidal involvement and peripheral sensorimotor neuropathy, speech problems and dysphagia).[142] The neurologic manifestations of "variant A-T" are more variable; first manifestations can occur later and cerebellar ataxia is not always present.[142] Extrapyramidal movement disorders are common in "variant A-T", though chorea and Parkinsonism are rare.[142, 143] Feeding and nutrition problems are less common in individuals with "variant A-T" than in those with “classic A-T”.[142]

Increased susceptibility to malignancy

Both “classic A-T” and "variant A-T" are associated with increased risk of developing malignancy, most notably lymphomas and leukaemia’s in children,[144] and in addition breast cancer, ovarian cancer, gastric cancer, liver cancer, oesophageal carcinomas, melanomas, leiomyomas, and sarcomas in adults.[141, 145]

Immunodeficiency, infection and pulmonary disease

Immunodeficiency is present in most individuals with “classic A-T” and is absent in individuals with “variant A-T”. Immunodeficiency is highly variable with abnormalities of humoral immunity, cellular immunity, or combined immune deficiency and, in most individuals, remains stable over time.[142] Mild sinopulmonary infections occur frequently in individuals with “classic A-T", but severe infections (bacterial, viral, and opportunistic) are uncommon. Pulmonary disease is present in most individuals with “classic A-T”, causing significant morbidity and mortality. Pulmonary disease can be attributed to a combination of recurrent infections, immune deficiency, aspiration, interstitial lung disease, and neurologic abnormalities.[142] Serum immunoglobulin levels and T- and B-cell counts are generally normal in individuals with “variant A-T”, respiratory infections occur at a frequency similar to the general population and pulmonary disease is not a major feature.[142]

Endocrine abnormalities

Endocrine abnormalities, including growth impairment, gonadal dysfunction, and insulin resistance, are common in individuals with “classic A-T”.[146] By contrast, the prevalence of endocrine abnormalities in people with “variant A-T” is thought to be similar to the general population.[142]

Cognition and behaviour

Deficits in intellectual functioning, nonverbal memory, verbal abstract reasoning and calculation, and executive function are thought to be an uncommon finding in individuals with “classic A-T”.[141] Where present, these deficits usually manifest at the end of the first decade of life.[142] No information is available on these findings in “variant A-T”.[142]

Trajectory and life expectancy

Life expectancy in “classic A-T” is significantly reduced in “classic A-T”, due to cancer, pulmonary disease, and infections; most individuals do not live longer than age 30 years. Life expectancy is longer in “variant A-T” and this has been attributed to less progressive neurologic decline, typical absence of respiratory and immunologic features, and later occurrence of malignancies.[142, 143] The majority of individuals with A-T require a wheelchair by adolescence. With time, individuals develop slurred speech and trouble moving their eyes from side to side (oculomotor apraxia), and telangiectases (tiny clusters of enlarged blood vessels that develop in the eyes and on the skin's surface). Whilst noting that there is no published evidence, the UK A-T guideline states that: *“many patients with mild variant A-T are known to be living into their 40s and 50s and some even into their 60s in the UK”*.[147]

Incidence and prevalence

Reported incidence of A-T varies between 1:300,000 and 1:40,000 live births. The estimated prevalence is 1-9:100,000.[141, 142] In the USA, approximately 350 children with A-T are known to the patient organisation A-T Children's Project.[148] The UK A-T society has estimated that, in the UK and Ireland, there are currently approximately 150 families with approximately 170 cases of A-T, giving a prevalence of approximately 1:400,000.[147] This guideline also note that milder “variant A-T” appears to be more common in the UK and Ireland (approximately 1 in 3 cases of A-T) than in other parts of the world (approximately 1 in 5 cases).[147]

Detection through newborn screening

It should be noted that A-T can only be identified by TREC-based NBS screening where immunodeficiency is present, i.e. in cases of “classic A-T”. It has been reported that TREC-based NBS screening for SCID probably identifies around 50% of children with “classic A-T”.[142].

The current systematic review included 9 retrospective reports of experience from implemented TREC-based NBS screening programmes for SCID,[19, 20, 22-25, 27-29] of which 7 reported details of non-SCID TCL screening outcomes.[20, 22-24, 27-29] Only 2two of these publications reported the identification of cases of A-T; the German screening programme identified 1 case over 3 years of screening (1,878,985 newborns screened)[28] and the California screening programme identified 5 cases over 6.5 years of screening (3,252,156 newborns screened).[27] The proportions of screen-positive, form these two programmes, which resulted in a diagnosis of A-T were 1/115 (0.87%)[28] and 5/212(2.36%).[27]

Establishing a diagnosis – genetic testing

A-T is caused by biallelic pathogenic variants in the A-T mutated (*ATM*) gene on chromosome 11q.26 and is inherited in an autosomal recessive manner.[142, 147] The diagnosis of A-T is established in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *ATM* identified by molecular genetic testing.[142] Molecular genetic testing can be based on a gene-targeted (single-gene testing, multigene panel), which requires determination of the gene(s) likely to be involved, or comprehensive genomic testing (exome sequencing, genome sequencing).

Targeted molecular genetic testing of at-risk relatives, for the *ATM* pathogenic variants identified in the proband may be considered appropriate in order to identify:

- Siblings with biallelic *ATM* pathogenic variants who could benefit from treatment of manifestations, surveillance for malignancy and awareness of agents/circumstances to avoid.
- Family members who are heterozygous for an *ATM* pathogenic variant and who could benefit from additional health surveillance.

Although heterozygous individuals are not at risk for A-T, their risk of developing cancer is increased compared to that of the general population. In particular, heterozygous females younger than age 50 years have an increased risk of developing breast cancer.[149]

Clinical guidelines

The A-T society and the A-T Specialist Centre at Nottingham University Hospitals NHS Trust have published guidance on the diagnosis and clinical care of children with A-T in the UK.[147]

Horizon scanning for new treatment options

We have searched clinical trials registries (ClinicalTrials.gov, EUCTR and ICTRP) for A-T, from 2017 to present, with the aim of identifying any un-published or ongoing studies of novel treatments for A-T for which early identification may be clinically relevant. Our searches retrieved a total of 33 entries, of which 22 related to trials of treatment. Most (18/22) entries for treatment trials concerned interventions for symptom management (intra-erythrocyte dexamethasone sodium phosphate, N-Acetyl-L-Leucine or complex home-based exercise intervention) and 1 concerned cancer treatment in A-T. Three trial entries concerned interventions which target the mechanisms of disease progression, in that they are intended to reduce DNA damage and mitochondrial dysfunction and/or stimulate DNA repair.[150, 151]

Our searches did not identify any studies of gene therapy in A-T, however, the ongoing UK study Trial REadiness in Ataxia Telangiectasia (TREAT-AT) aims to optimise outcome measures in A-T to facilitate future clinical trials, noting that: *"Antisense oligonucleotide (ASO) therapies present a promising disease-modifying treatment. A deep intronic ATM splice-variant c.5763-1050A>G (among others) is an excellent ASO target, but the lack of validated outcome measures and biomarkers hampers clinical trial evaluation."*[152]

Dedicator of cytokinesis 8 protein (DOCK8) deficiency

Clinical characteristics

Dedicator of cytokinesis 8 protein (DOCK8) deficiency is a rare and severe form of combined immunodeficiency with a variety of clinical features including severe skin and lung features, recurrent frequently severe/life-threatening infections, allergic diseases (eczema and food allergy), autoimmunity, and a high risk of malignancy (particularly virally-driven cancers).[153, 154] DOCK8 deficiency usually presents at a young age, ranging from the first months to early years of life.[153]

DOCK8 deficiency has been identified as the underlying abnormality in the majority of patients with autosomal recessive Hyper IgE Syndrome (AR-HIES). DOCK8 deficiency shares some features (e.g. eosinophilia, elevated serum IgE levels, and recurrent staphylococcal infections) with the autosomal dominant form (AD-HIES), which is caused by signal transducer and activator of transcription 3 (*STAT3*) mutations. However, DOCK8 deficiency is recognised as a unique entity with distinct clinical and immunological features; patients with AD-HIES do not suffer from environmental or food allergies.[153]

Infections

Cutaneous viral infections, including Varicella zoster, Molluscum contagiosum, Herpes simplex, and Human Papilloma viruses, are common in patients with DOCK8 deficiency; these infections may be severe, persistent, and refractory to treatment.[153]

Documented non-cutaneous viral infections include meningitis, encephalitis, keratitis, retinitis, blepharoconjunctivitis, periodontitis, pneumonia, hepatitis and enteritis involving many different viruses (e.g. cytomegalovirus, Epstein Barr Virus [EBV], rotavirus, Herpes simplex virus, hepatitis A, B and C viruses).[153]

Patients with DOCK8 deficiency also experience both superficial and/or localised, and invasive bacterial infections. Patients often experience recurrent sinopulmonary bacterial infections that can lead to bronchiectasis.[153, 154] Cutaneous bacterial infections with *Staphylococcus aureus*, are common.[153]

Bacterial or fungal abscesses have been identified in the skin, liver, kidney, lung and brain;[153] a retrospective review of 136 patients with DOCK8 deficiency, by Aydin et al. 2015 reported that 62% had experienced abscesses, of which 84% were to the skin, 7% affecyed internal organs and 5% were intracranial.[154]

Reported fungal infections range from mucocutaneous candidiasis to invasive disease with organisms such as *Aspergillus*, and less commonly, *Cryptococcus neoformans*.[153]

The Aydin et al. 2015 review reported that 58% of patients with DOCK8 deficiency had experienced a life-threatening infection, of which 42% were bacterial, 23% viral, 16% fungal, 1% protozoan and 18% unknown.[154]

Autoimmune disease

Patients with DOCK8 deficiency may also suffer from autoimmune disorders, including autoimmune haemolytic anaemia, chorioretinitis/uveitis, hypothyroidism, and cytopenias and vasculitis; systemic lupus erythematosus has been reported in 1 patient.[153] Autoimmunity has been reported to affect 13% of patients.[154]

Increased susceptibility to malignancy

The immune defects caused by DOCK8 deficiency also lead to an increased risk of cancer, reported to affect 17% of patients.[154] Malignancies are commonly virally-driven (e.g. squamous cell carcinomas related to Human Papillomavirus infection and EBV-driven smooth muscle tumours and lymphomas.[153]

Trajectory and life expectancy

DOCK8 deficiency is associated with high morbidity and mortality. A retrospective review of data from 136 patients reported a decline in overall probability of survival from 87% to 37% at 10 and 30 years, respectively.[154] The cumulative incidence of life-threatening infections, cerebral events and malignancies was 88%, 32% and 48% at 30 years of age.[154] Death in patients with DOCK8 deficiency has been reported to occur from infection, malignancies and, less commonly, vasculitis and progressive multifocal leukencephalopathy.[153, 154]

Incidence and prevalence

The prevalence of DOCK8 is uncertain; a 2017 review article, by Briggs et al. 2017 reported that a total of 230 cases had been described at the time of publication.[153] The majority of patients with DOCK8 deficiency are of Turkish and Arabic descent, populations in which consanguinity rates are high, however, cases have also been documented in North and South America, Europe and China.[153]

Detection through newborn screening

A study of 2 brothers and a sister who had AR-HIES, born to consanguineous parents, applied the TREC assay to fresh blood samples dotted onto a newborn screening filter and found low TRECs in the 13-month old child and undetectable TRECs in the 2 older siblings (4 and 6 years).[155] These findings suggest that patients with DOCK8 deficiency may be detected by NBS screening for SCID, however, since NBS samples were not available for testing in this study, the extent to which new T-cell production and/or efflux from the thymus may be impaired in the newborn and/or decline with age is unclear.

The current systematic review included 9 retrospective reports of experience from implemented TREC-based NBS screening programmes for SCID,[19, 20, 22-25, 27-29] of which 7 reported details of non-SCID TCL screening outcomes.[20, 22-24, 27-29] None of these publications reported identification of a case of DOCK8 deficiency.

Establishing a diagnosis – genetic testing

DOCK8 deficiency is diagnosed based on clinical features in combination with suggestive immunologic laboratory findings and confirmatory genetic analysis. Laboratory/immunological findings supportive of a DOCK8 deficiency diagnosis

include eosinophilia, elevated IgE levels, impaired vaccine titre responses, low naïve CD4+ T-cell count, an exhausted cytotoxic T-cell panel with elevated percentages of effector memory RA (TEMRA)+ CD8+ T-cells, and low switched and unswitched memory B-cells.[153] DOCK8 protein expression can be assessed using flow cytometry or western blot analysis, however, in patients with mutations that allow for somatic reversion, DOCK8 may be expressed up to normal levels in the majority of T-cells, with minimal reversion in B-cells. Evaluation of DOCK8 expression in a range of immune cell types has therefore been suggested and, in cases where there is a strong suspicion for DOCK8 deficiency, confirmatory sequencing of DNA from (e.g. saliva, neutrophils or fibroblasts) has been recommended.[153]

Clinical guidelines

Our searches have not identified any clinical guidelines relating to DOCK8 deficiency. The 2017 review article, by Briggs et al. 2017 noted that HSCT represents the only curative treatment for DOCK8 deficiency.[153]

Horizon scanning for new treatment options

We have searched clinical trials registries (ClinicalTrials.gov, EUCTR and ICTRP) for DOCK8 deficiency, from 2017 to present, with the aim of identifying any un-published or ongoing studies of novel treatments for DOCK8 deficiency for which early identification may be clinically relevant. Our searches did not identify any studies of treatments for DOCK8 deficiency.

Congenital athymia

Clinical and genetic characteristics

Congenital athymia is a rare, life-limiting disorder arising from inborn errors of immunity which cause impaired thymus development or abnormal development of thymic stromal cell development and function. Most infants with congenital athymia have 22q11.2 DS or CHARGE syndrome, and other pathogenic mutations include *TBX1* deficiency, *TBX2* deficiency, *FOX13* haploinsufficiency, *FOXN1* deficiency and *PAX1* deficiency. Other potential causes of abnormal thymic development are *in utero* exposure to poorly controlled maternal diabetes, alcohol and under or over exposure to retinoic acid. Infants with athymia have severe TCL and are highly susceptible to infections and autoimmunity. Defects of thymus development are associated with additional abnormalities affecting multiple organs, e.g. craniofacial, heart, major blood vessels, parathyroid. Infants with congenital athymia will typically present, within the first few months of life, with failure to thrive and persistent, severe infections, (e.g. *pneumocystis jirovecii* pneumonia, CMV, persistent respiratory of gastrointestinal viral infections, persistent candidiasis). Symptoms of immune dysregulation (e.g. erythroderma, hepatosplenomegaly, lymphadenopathy) or autoimmunity (e.g. haematologic cytopenias) can also occur. In addition, infants may present with clinical features which related to the underlying syndrome rather than complications of severe TCL, (e.g. parathyroid hyperplasia manifesting as hypocalcaemia and neonatal seizures, cardiac conotruncal outflow defects leading to CHD). Patients with CHARGE syndrome may have coloboma, atresia choanae, growth/developmental retardation, genitourinary and/or ear anomalies, and cranial nerve dysfunction.[156-158]

Trajectory and life expectancy

Untreated congenital athymia is incompatible with long-term survival.[157]

Incidence and prevalence

Estimates of the incidence of 22q11.2 DS vary (see above) and, although 22q11.2 DS is amongst the most common causes of congenital athymia, congenital athymia remains uncommon in this group (≤1% of individuals).[157] The incidence of CHARGE syndrome is approximately 1 in 10,000 to 17,000 live births and the frequency of congenital athymia amongst infants with CHARGE syndrome is unknown.[157]

Detection through newborn screening

In patients with congenital athymia, severe TCL is detectable as an abnormal on TREC-based NBS screening for SCID. However, such abnormal screening results may not always be recognised as congenital athymia, particularly where the cause is not genetically defined.[158] Increasing use of next-generation sequencing (NGS) may facilitate increased recognition of athymia with a genetic aetiology. However, the clinic and genetic heterogeneity of the condition mean that timely diagnosis remains challenging, with recognition of congenital athymia sometimes occurring only after failure of naïve T-lymphocyte reconstitution following HSCT for suspected genetically undefined SCID.[157] There is some evidence to indicate that the introduction of NBS screening for SCID may be associated with increased detection of congenital athymia: During the first 2.5 years of the NBS screening programme for SCID in Germany, 7 patients with congenital athymia were identified and referred for thymus transplantation at Great Ormond Street Hospital, London, UK, compared with 3 referrals from Germany in the preceding ten years.[28, 157]

The current systematic review included 9 retrospective reports of experience from implemented TREC-based NBS screening programmes for SCID,[19, 20, 22-25, 27-29] of which 7 reported details of non-SCID TCL screening outcomes.[20, 22-24, 27-29] Only 3 of these publications reported sufficient information to identify cases of congenital athymia; the German screening programme identified 7 cases over 3 years of screening (1,878,985 newborns screened)[28, 157] the New Zealand screening programme identified 2 cases (1 CHARGE-associated congenital athymia and 1 complete 22q11.2 DS) over 3 years of screening (191,075 newborns screened)[23] and in Israel 2 cases of complete 22q11.2 DS were identified over 5 years (937,953 newborns screened).[24] The proportions of screen-positive, from these two programmes, which resulted in a diagnosis of congenital athymia were 7/115 (6.09%)[28] 2/21 (9.52%),[23] and 2/105 (1.90%)[24]

Establishing a diagnosis – genetic testing

Thorough immunological investigation, including full blood count, T-cell, B-cell and NK-cell quantification, thymic output (naïve versus memory T-lymphocytes, RTEs, TRECs) and T-lymphocyte quality (proliferation, T-cell receptor repertoire analysis, serum immunoglobulins), in addition to genetic testing, is important to distinguish between patients with haematopoietic cell-intrinsic SCID and congenital athymia before considering HSCT as a treatment strategy.[157] Although NGS may be helpful in identifying known pathogenic mutations, there remain a proportion of patients with a SCID-like immunophenotype who do not have a genetic diagnosis.[159]

Clinical guidelines

Our searches have identified an in-press article reporting guidelines for the management of patients with congenital athymia, from the European Society for Immunodeficiencies.[157] This guideline lists the following indications to suspect congenial athymia:

- Very low/absent TREC on NBS screening for SCID
- Clinical features of severe TCL (persistent opportunistic severe infection, failure to thrive)
- Omenn syndrome-like features
- Autoimmunity (particularly cytopenias)
- Lymphopenia in the presence of relevant syndromic features (see Clinical characteristics, above)
- Family history of congenitl athymia
- Genetically undefined T-B+NK+ immunotype
- Failure of naïve T-cell reconstitution following HSCT

The guideline emphasises the need for early identification of congenital athymia in order to guide appropriate treatment selection. It is important to distinguish between patients with haematopoietic cell-intrinsic SCID, who can benefit from HSCT, and congenital athymia, where HSCT outcomes are very poor.[158] Allogenic thymus transplantation is the main treatment for congenital athymia, accompanied by supportive care particularly during the pre-transplant period (isolation, anti-microbial prophylaxis, immunoglobulin replacement therapy, no live vaccines, irradiated CMV-negative blood products, no breast feeding from CMV seropositive mothers, immunosuppression for Omenn-like phenotype, family support) and patients should be referred to a specialist centre as soon as possible.[157] Thymus transplantation is currently only offered by Duke University Medical Centre in the US and Great Ormond Street Hospital in the UK; more than 150 patients have been transplanted to date, across both centres, with a similar OS of around 75%.[158] Mortality has been reported as being closely

related to pre-existing infections and usually occurring during the first year after transplantation.[158] Tissue preparation and transplantation techniques are similar in the two programmes, however, in the US, thymus transplantation has recently been approved as a medicinal product by the Food and Drugs Administration (FDA) and is now known as Rethymic®.[160]

Horizon scanning for new treatment options

We have searched clinical trials registries (ClinicalTrials.gov, EUCTR and ictrp) for athymia deficiency, from 2017 to present, with the aim of identifying any un-published or ongoing studies of novel treatments for which early identification may be clinically relevant. Our searches identified a US registry study to follow the long-term outcomes of patients treated with Rethymic® (thymic transplantation).[161] [162] Our searches did not identify any studies of new treatments for congenital athymia.

Cartilage hair hypoplasia (CHH)

Clinical and genetic characteristics

CHH is a skeletal dysplasia with autosomal recessive inheritance, caused by mutations in the ribonuclease mitochondrial RNA-processing (*RMRP*) gene. Common morphological features of the disorder include short stature with short or deformed limbs and short fingers, chest deformity, hypermobility of the joints, and fine sparse or fragile hair. X-rays usually show metaphyseal lesions and large round epiphyses during childhood.[163] [164] CHH is associated with varying degrees of immunodeficiency, autoimmune complications, Hirschsprung disease and associated enterocolitis, anaemia, increased risk of malignancy, impaired spermatogenesis, and delayed puberty in girls.[163, 165]

Impairment of immune function constitutes the greatest health risk for people with CHH. Individuals with CHH may have variable types (e.g. lymphopenia, defects in T-cell function/proliferation, defects in B lymphocyte proliferation, low IgG, undetectable IgA) and severity of immunodeficiency. Deficient cellular immunity is very common (88%) in individuals with CHH, however this is not always associated with increased rates of infection (35% to 65% of individuals, usually during infancy and childhood). Bronchiectasis has been reported in 29% to 52% of individuals with CHH, however, clinical relevance and progression is variable.[165]

Clinical autoimmunity is common in individuals with CHH. Autoimmune complications and severe allergic reaction are rare, however, the pathophysiology of autoimmunity in CHH is unknown.[165]

Deficient erythropoiesis can lead to anaemia in individuals with CHH. Mild anaemia is common (80%) and resolves spontaneously, during childhood, in most individuals. Severe, persistent anaemia is seen in approximately 6% of individuals, around 50% to 75% of whom require life-long transfusions or bone marrow transplant.[165]

Long-term (39-year) follow-up of a Finnish cohort of patients with CHH showd that 14/123 (11%) developed a malignancy. The most frequently occurring cancers, in patients with CHH, are non-Hodgkin lymphoma, squamous cell carcinoma, leukemia, and Hodgkin lymphoma. Risk of malignancy is not correlated with pathogenic *RMRP* variant or severity of immunodeficiency.[165]

Variability in presentation and uncertainty around pathogenesis mean that surveillance for immunodeficiency, malignancy and autoimmune disease is important for all individuals with CHH. Administration of live vaccines is not recommended unless normal T-cell responses have been demonstrated. HSCT can correct immunodeficiency in the context of CHH, but does not improve musculoskeletal or other growth-related features of the syndrome.[163] There is no curative treatment for CHH, multi-disciplinary supportive care aims to increase function, reduce complications and improve quality of life.[165]

Incidence and prevalence

CHH occurs most commonly in the Old Order Amish population, where the incidence is approximately 1 in 1,300 newborns (carrier frequency 1 in 10), and in people of Finnish descent, where the incidence is approximately 1 in 20,000 newborns (carrier frequency 1 in 76). The condition is rare outside these populations; cases have been reported in individuals of European and Japanese descent, but incidence is unknown.[164, 166] [165]

Detection through newborn screening

TREC-based NBS screening for SCID can identify individuals with CHH where TCL is present.[165]

The current systematic review included 9 retrospective reports of experience from implemented TREC-based NBS screening programmes for SCID,[19, 20, 22-25, 27-29] of which 7 reported details of non-SCID TCL screening outcomes.[20, 22-24, 27-29] Only 1 of these publications, a report of the first 5 years of the Japanese screening programme (137,484 newborns screened), explicitly reported diagnoses (n=2) of CHH.[29] Three further publications reported cases of SCID and non-SCID TCL in which a pathogenic variant of *RMRP* was identified; the German screening programme identified 3 cases over 3 years of screening (1,878,985 newborns screened)[28] the California screening programme identified 1 case over 7 years of screening (3,252,156 newborns screened)[27] and in Israel 1 case was identified over 5 years (937,953 newborns screened).[24] The proportions of screen-positive which resulted in a diagnosis of CHH or in which a pathogenic variant of *RMRP* was identified were 2/78 (2.56%),[29] 2/212 (0.47%),[27] and 1/105 (0.95%).[24]

Establishing a diagnosis – genetic testing

Where clinical and radiographic findings are suggestive of CHH, the diagnosis can be confirmed by genetic testing to identify pathogenic or likely pathogenic variants in *RMRP*. Identification of biallelic *RMRP* variants of uncertain significance (or of 1 known *RMRP* pathogenic variant and 1 *RMRP* variant of uncertain significance) does not confirm or rule out the diagnosis. Genetic testing can use gene-targeted methods (single-gene testing or multi-gene panel), where phenotypic and radiographic findings allow the clinician to determine which gene(s) are likely to be involved, or comprehensive genomic testing (exome sequencing or genome sequencing), where the phenotype is not readily distinguishable from other inherited disorders that are characterised by short stature. Once *RMRP* pathogenic variants have been identified, carrier testing for at-risk family members and molecular genetic prenatal and pre-implantation testing for CH are possible.[165]

Clinical guidelines

Our searches have not identified any clinical guidelines relating to CHH.

Horizon scanning for new treatment options

We have searched clinical trials registries (ClinicalTrials.gov, EUCTR and ictrp) for athymia deficiency, from 2017 to present, with the aim of identifying any un-published or ongoing studies of novel treatments for which early identification may be clinically relevant. Our searches did not identify any studies of new treatments for CHH.

Appendix 5 – Horizon scanning for new treatment options

As noted in Appendix 4, horizon scanning did not identify any reports of novel, disease modifying treatments or 22q11.2 DS, DOCK8 deficiency, congenital athymia or CHH. Similarly, no reports of gene therapy in A-T were identified. One ongoing UK study TREAT-AT was identified, which aims to optimise outcome measures in A-T to facilitate future clinical trials, noting that: *"Antisense oligonucleotide (ASO) therapies present a promising disease-modifying treatment. A deep intronic ATM splice-variant c.5763-1050A>G (among others) is an excellent ASO target, but the lack of validated outcome measures and biomarkers hampers clinical trial evaluation."*[152]

With respect to gene therapies for SCID, in 2018, the NICE HST7 made the following recommendation on the use of Strimvelis® for the treatment of patients with ADA SCID: *'Strimvelis is recommended, within its marketing authorisation, as an option for treating adenosine deaminase deficiency–severe combined immunodeficiency (ADA–SCID) when no suitable human leukocyte antigen-matched related stem cell donor is available.'*[167] An observational registry has been established, in Italy, to monitor the safety and efficacy of Strimvelis® in up to 50 patients over a minimum of 15 years.[168]

Our searches identified a further five publications, reporting the results of clinical studies for gene therapies for SCID:

Cicalese et al. 2018 reported a safety analysis for 18 patients with ADA SCID, enrolled in single arm open-label studies or compassionate use programmes, who had received gene therapy with an autologous $CD34^+$-enriched cell fraction that contains $CD34^+$ cells transduced with a retroviral vector encoding the human ADA cDNA sequence. The median age of patients, at gene therapy, was 1.7 years (range: 0.5 to 6.1 years) and the median duration of follow-up was 6.9 years (range: 2.3 to 13.4 years). Survival was 100%. Adverse events (AEs) were mostly grade 1 or grade 2 and were reported by all 18 patients following gene therapy. Thirty-nine serious adverse events (SAEs) were reported by 15 of 18 patients; no SAEs were considered related to gene therapy.[169]

Mamcarz et al. 2019 reported a phase 1-2 study of a lentiviral vector to transfer *IL2RG* complementary DNA to bone marrow stem cells after low-exposure, targeted busulfan conditioning in 8 infants with newly diagnosed X-linked SCID. The median follow-up duration was 16.4 months. In 7 infants, the numbers of CD3+, CD4+, and naive CD4+ T-cells and NK-cells normalised by 3 to 4 months post-infusion. Previous infections resolved in all infants, and all continued to grow normally. Four infants were able to discontinue immunoglobulin therapy and 3 of these infants responded to vaccines.[170]

Kohn et al. 2021 reported combined data from two prospective, non-randomised, phase 1–2 clinical studies conducted in the US (NCT01852071 and NCT02999984) and a third non-randomised, prospective, phase 1–2 clinical study conducted in the UK (NCT01380990). These studies aimed to assess the safety and efficacy of an autologous investigational lentiviral vector–mediated gene therapy (OLT-101) composed of CD34+ HSPCs genetically modified *ex vivo* with EFS-ADA LV in patients with ADA SCID. The US studies included children with a diagnosis of ADA

SCID who were ≥1 month of age and who lacked a HLA-matched sibling, whilst for the UK study children with a diagnosis of ADA SCID were eligible for inclusion if they were <5 years of age or aged 5 to 15 years with preserved thymic function. In total, 50 children (30 in the US and 20 in the UK) were treated between 2012 and 2016. Overall, survival at 24 and 36 months was 100%. Patients had sustained normalisation of ADA levels. With respect to immune reconstitution, 90% of patients in the US and 100% of patients in the UK were able to discontinue immunoglobulin replacement therapy by 24 and 26 months, respectively.[171] The NICE website lists evaluation of OLT-101 as awaiting development.[172]

Reinhardt et al. 2021 reported the results of a small cohort study (NCT00794508) of ten ADA SCID patients, aged 3 months to 15 years, who underwent gene therapy between 2009 and 2012. Treatment comprised transplantation with autologous $CD34^+$ cells, transduced *ex vivo* with the myeloproliferative sarcoma virus, negative control region deleted, dl587rev primer binding site (MND) - ADA gammaretroviral vector (gRV) and infused following busulfan reduced-intensity conditioning. Patients were followed-up over 8 to 11 years. Nine patients had sufficient immune reconstitution and did not require resumption of enzyme replacement therapy or secondary HSCT. Four patients remain off immunoglobulin replacement therapy and responded to vaccinations.[113]

Cowan et al. 2022 reported the results of a phase 1–2 clinical study (NCT03538899) of the transfusion of autologous CD34+ cells, transfected with a lentiviral vector containing *DCLRE1C*, in 10 infants with newly diagnosed Artemis-deficient SCID (ART SCID). Five of 6 patients who were followed-up for at least 24 months had T-cell reconstitution at a median of 12 moths. All ten patients were healthy at the time of the report.[173]

All other studies of developments in gene therapy, identified through horizon scanning searches, were early stage *in vitro* or animal studies,[174, 175 176-186] or phase 1-2 studies that did not report clinical outcomes.[187]

Appendix 6 – Current newborn screening landscape for SCID

This Appendix provides an overview of international screening practice for SCID. The 2023 HIQA, Republic of Ireland report included findings from a scoping search to determine practice in 34 countries considered to be most relevant to the Republic of Ireland, including countries in the European Economic Area, the UK, the US, Canada, Australia and New Zealand.[1] This selection of countries is also likely to be most relevant to the UK and findings from the HIQA report are therefore summarised and updated in Table 39.

Table 39: Summary of current newborn screening landscape for SCID

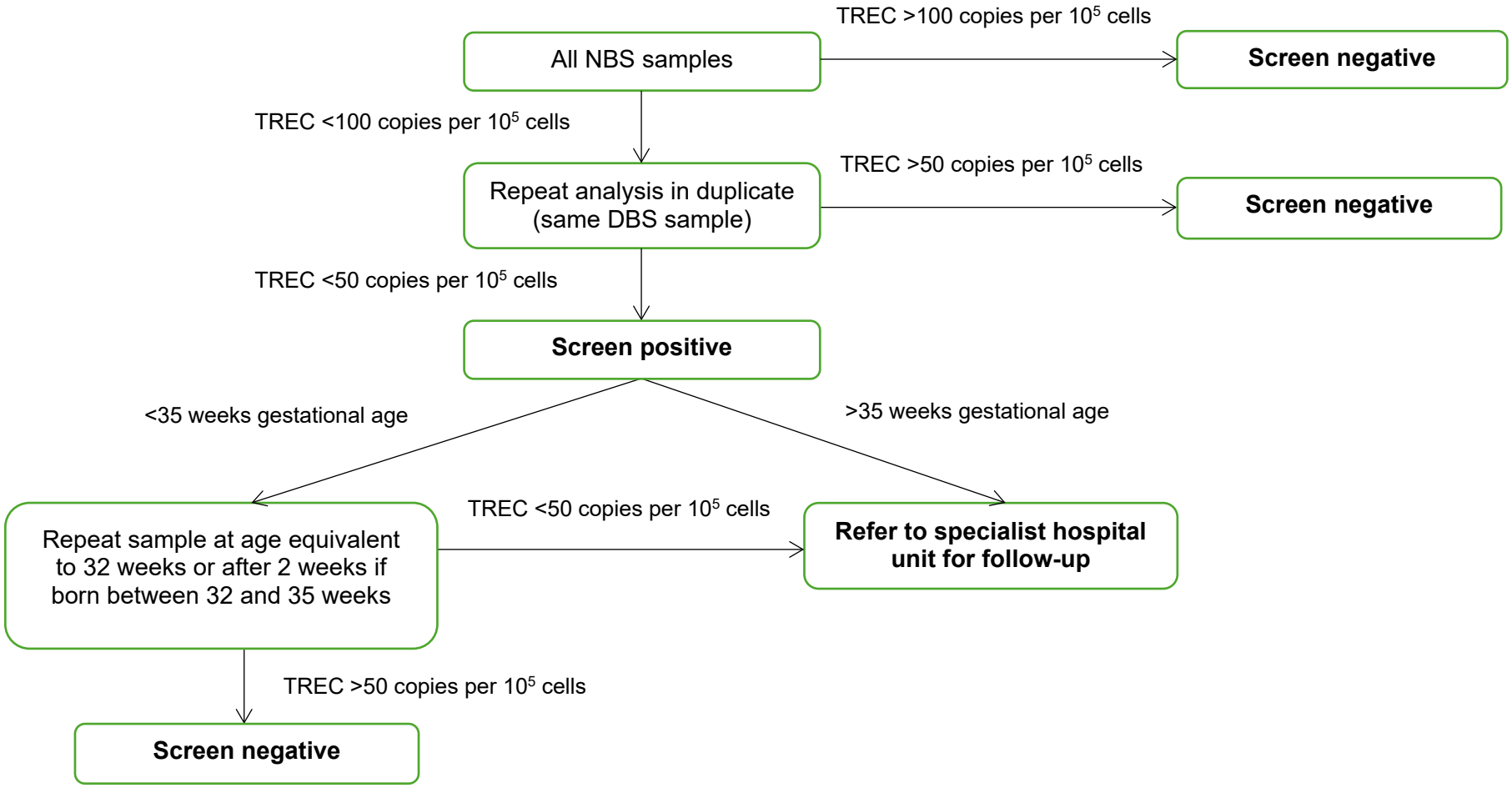
Country (Province, Territory or State)	Status of NBS screening for SCID
Australia (all)	Implemented (various dates 2022-2024) What is screened in the program | Australian Government Department of Health and Aged Care
Austria	Implemented[188, 189]
Belgium	implementation beginning (2023)[189]
Bulgaria	Pilot (2022)[26]
Canada (Alberta)	Implemented (2019)
Canada (British Columbia)	Implemented (2022) Disorders Screened (perinatalservicesbc.ca)
Canada (Manitoba)	Implemented https://sharedhealthmb.ca/services/diagnostic/cpl/newborn-screening/
Canada (New Brunswick)	Implemented (2016)
Canada (Nova Scotia)	Implemented (2016)
Canada (Prince Edward Island)	Implemented (2016)
Canada (Newfoundland and Labrador)	Not currently screened for[189]
Canada (Ontario)	Implemented (2013)
Canada (Quebec)	Implemented (2023) https://www.quebec.ca/en/health/health-issues/a-z/severe-combined-immunodeficiency
Canada (Saskatchewan)	Recommended (2022)[189]
Croatia	Not currently screened for[189] Public information on neonatal screening (kbc-zagreb.hr)
Cyprus	Not currently screened for[189] Neonatal Screening Program (cpp.org.cy)
Czech republic	Implemented (2024)[190] https://www.med.muni.cz/en/research-and-development/research-and-development/publishing/publikace-lf-mu/2436161
Denmark	Implemented (2020)
Estonia	Not currently screened for[189]
Finland	Partially implemented[189, 191]
France	Pilot[189] Not currently available nationally[192]
Germany	Implemented (2019)
Greece	Not currently screened for[189]
Hungary	Not currently screened for[189]

Iceland	Implemented (2017)
Italy	Regional implementation and pilot[189] https://www.aismme.org/extended-newborn-screening.html
Latvia	Implemented[188, 189]
Lithuania	Not currently screened for[189]
Luxemburg	Not currently screened for[189]
Malta	Not currently screened for[189]
The Netherlands	Implemented (2021)
New Zealand	Implemented (2017)
Norway	Implemented (2018)
Poland	Regional implementation pilot
Portugal	Not currently screened for[189]
Romania	Not currently screened for[189]
Slovakia	Under implementation (2024) https://www.sma-screening-alliance.org/news/slovakia-is-in-the-process-of-starting-routine-newborn-screening-for-sma
Slovenia	Unclear: Under evaluation and pilot[188] Planned implementation[193] Implemented[189]
Spain	Regional implementation/pilot
Sweden	Implemented (2019)
Switzerland	Implemented (2019)
United Kingdom	Under evaluation and pilot (2024)
United States (all)	Implemented (various dates 2010-2018)

The following pages summarise the algorithms used in implemented NBS screening for SCID screening programmes, reported in publications included in this evidence summary. We have included one additional algorithm, for the screening programme implemented in Catalonia, Spain,[7] which was reported in a publication identified by our searches and previously included in the HIQA report.[1] For ease of reading, the screening algorithms used by individual programmes are represented as flow charts; it should be noted that these flow charts have been constructed using only the information reported in the publications cited.

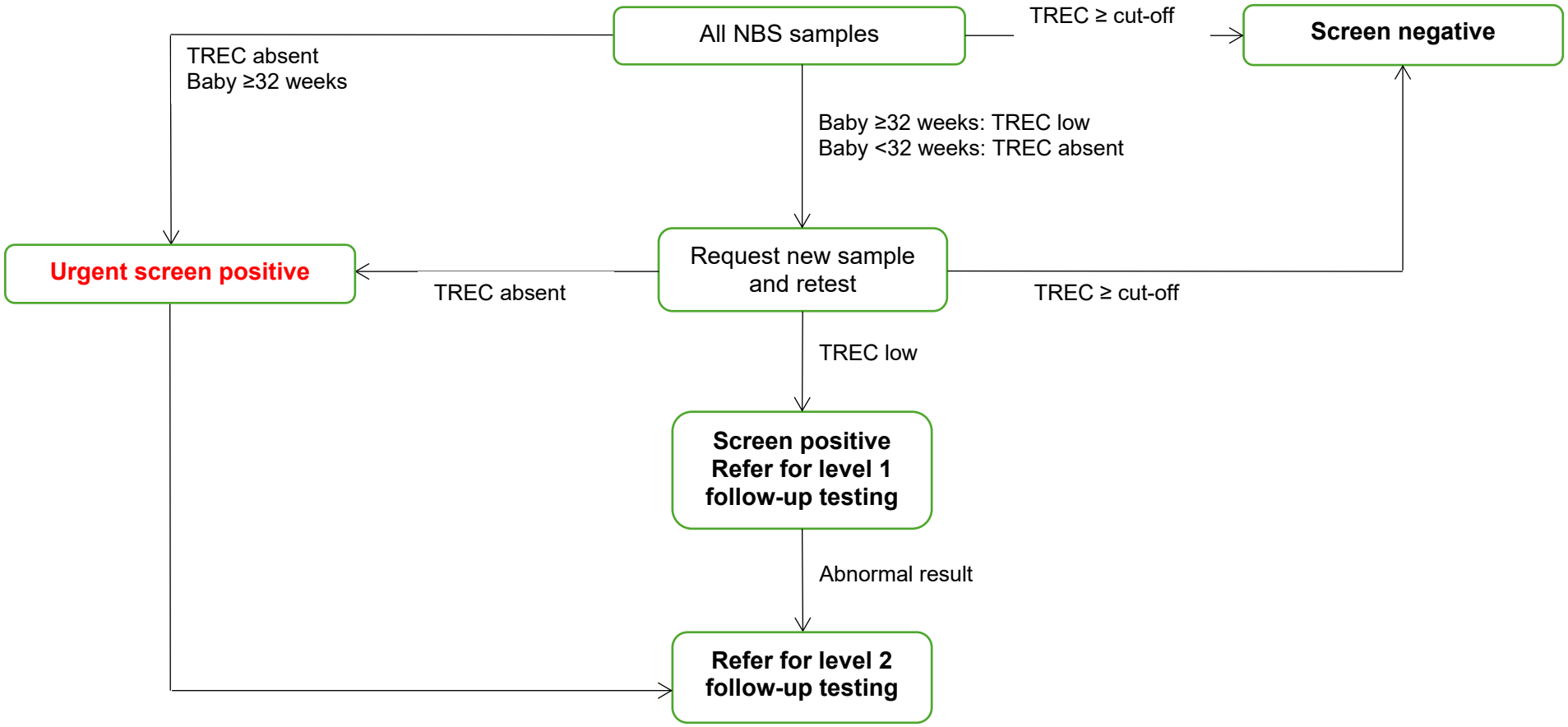
Denmark

Screening for SCID was added to the Danish NBS screening programme on 1 February 2020. The screening programme utilises TREC levels in DBS samples from heel pricks, determined using a commercial RT-PCR kit, EONIS™ PCR kit (Perkin Elmer, Turku, Finland).[19]



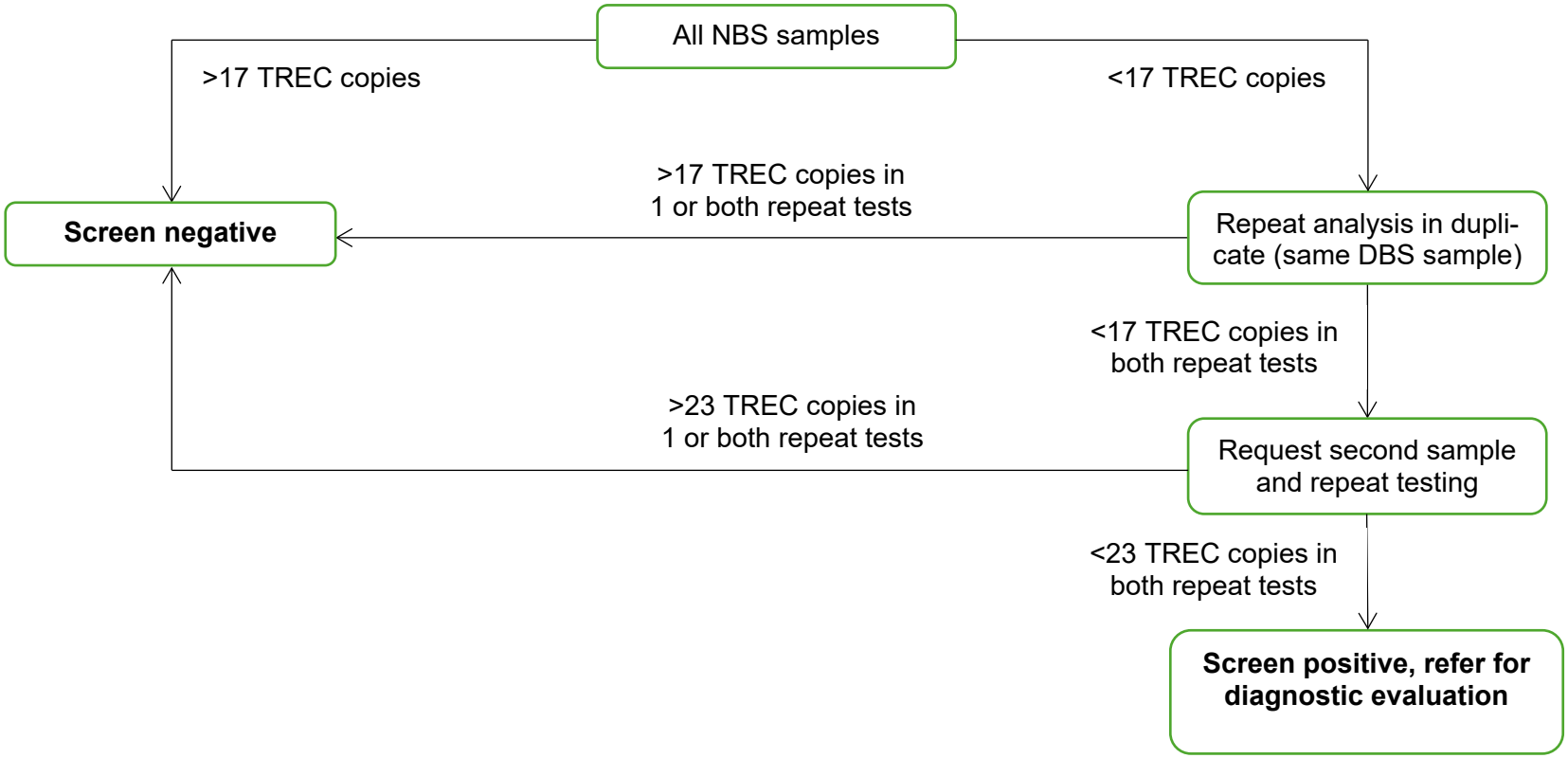
Germany

Screening for SCID was added to the Germany NBS screening programme in August 2019. The screening programme utilises TREC levels in DBS samples from heel pricks, determined using a commercial RT-PCR kits EnLite™ Neonatal TREC kit (Perkin Elmer, Finland) or SPOT-it™ (ImmunoIVD, Sweden) or in-house platforms.[28]



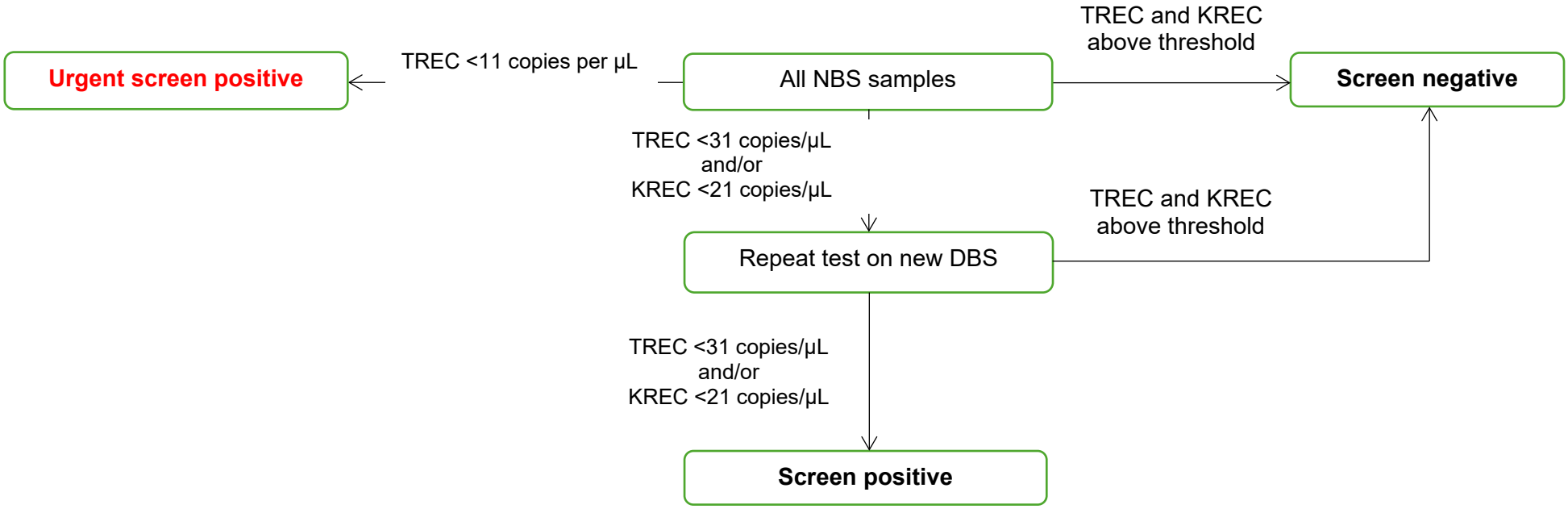
Israel

Screening for SCID was added to the Israel NBS screening programme on 1st October 2015. The screening programme utilises TREC levels in DBS samples from heel pricks, determined using a commercial Realtime PCR kit, EnLite™ Neonatal TREC kit (Perkin Elmer, UK).[24]



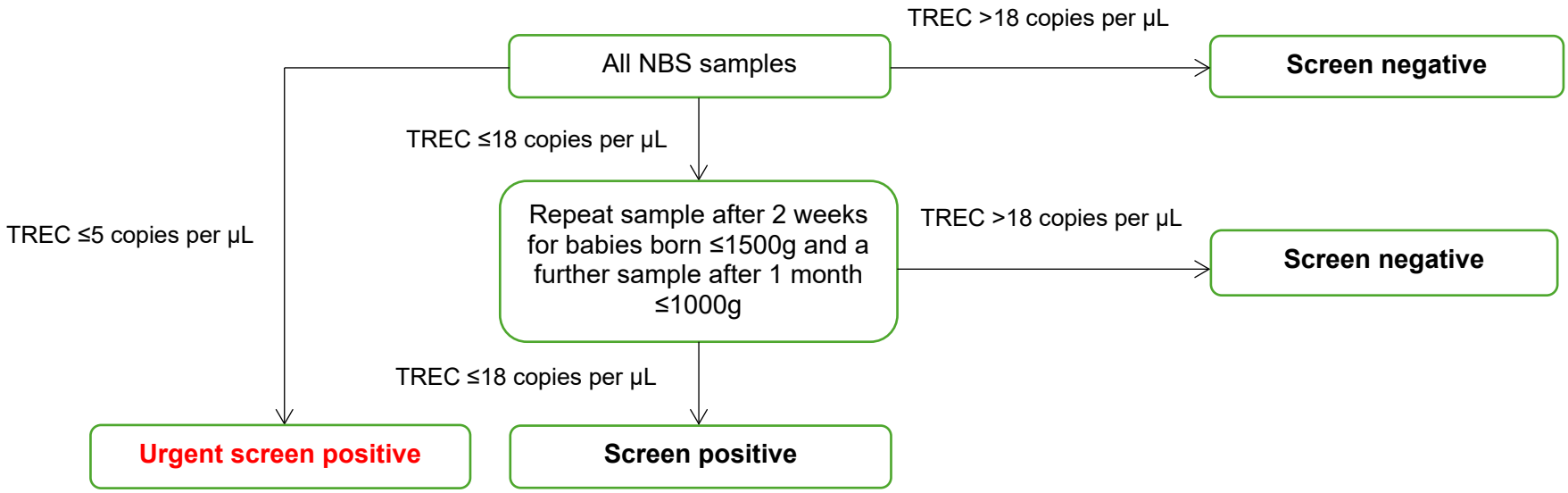
Japan

Screening for SCID was added to the Japan NBS screening programme, in the Aichi Prefecture, on 1st April 2017. In its first 3 years, the screening programme utilised TREC levels in DBS samples from heel pricks, changing to TREC/KREC levels in April 2020. TREC/KREC levels are determined using a commercial RT-PCR kit, EnLite™ TREC kit for the first 3 years then EnLite™ TREC/KREC kit (Perkin Elmer, Finland).[29]



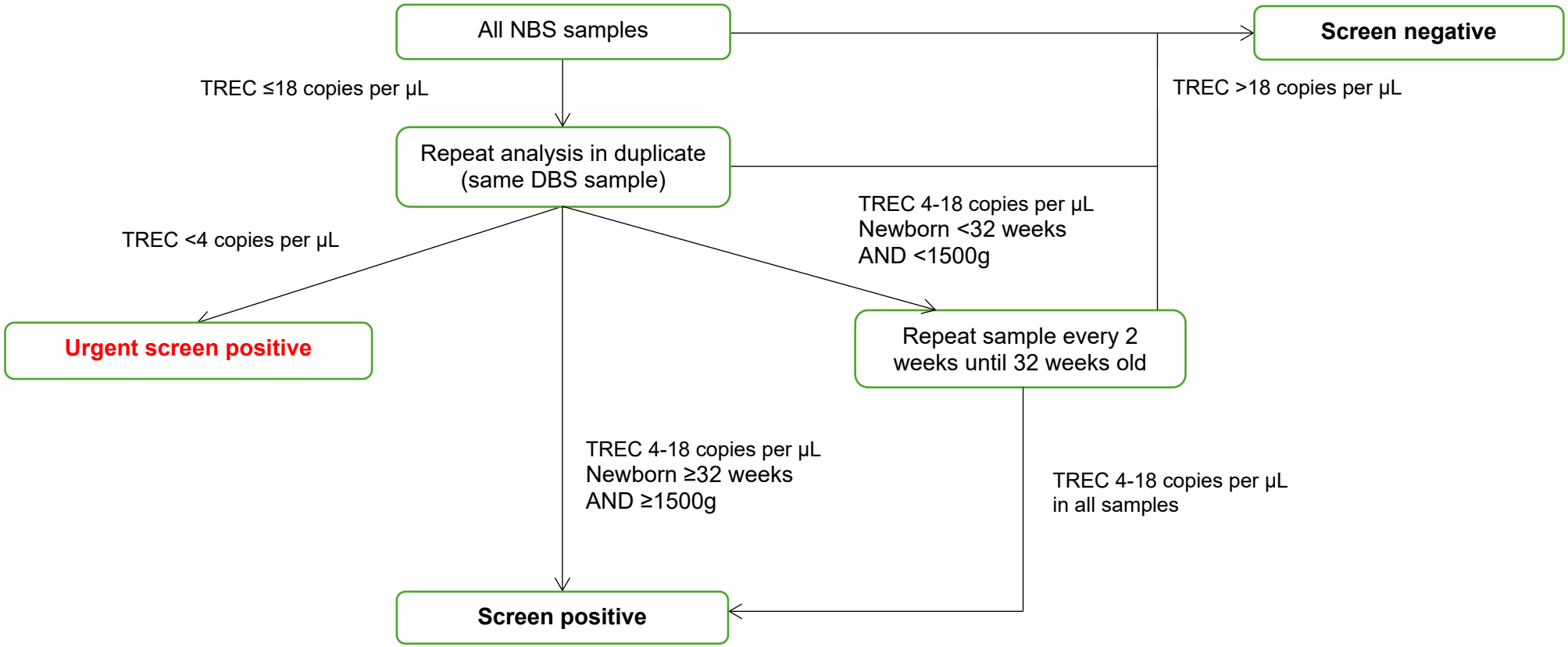
New Zealand

Screening for SCID was added to the New Zealand NBS screening programme on 1st December 2017. The screening programme utilises TREC levels in DBS samples from heel pricks, determined using a commercial RT-PCR kit, EONIS™ PCR kit (Perkin Elmer, Turku, Finland).[23]



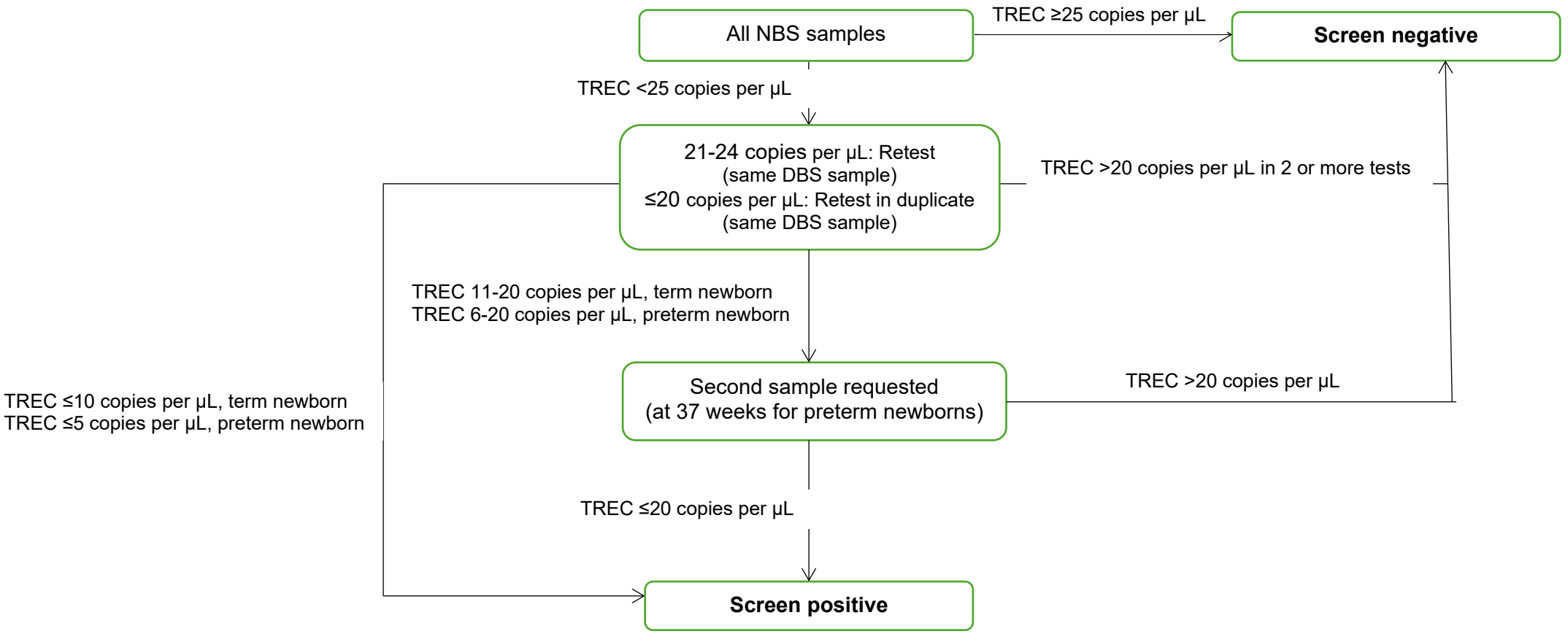
Singapore

Screening for SCID was added to the Singapore NBS screening programme on 10th October 2019. The screening programme utilises TREC levels in DBS samples from heel pricks, determined using a commercial RT-PCR kit, EONIS™ PCR kit (Perkin Elmer, Turku, Finland).[22]



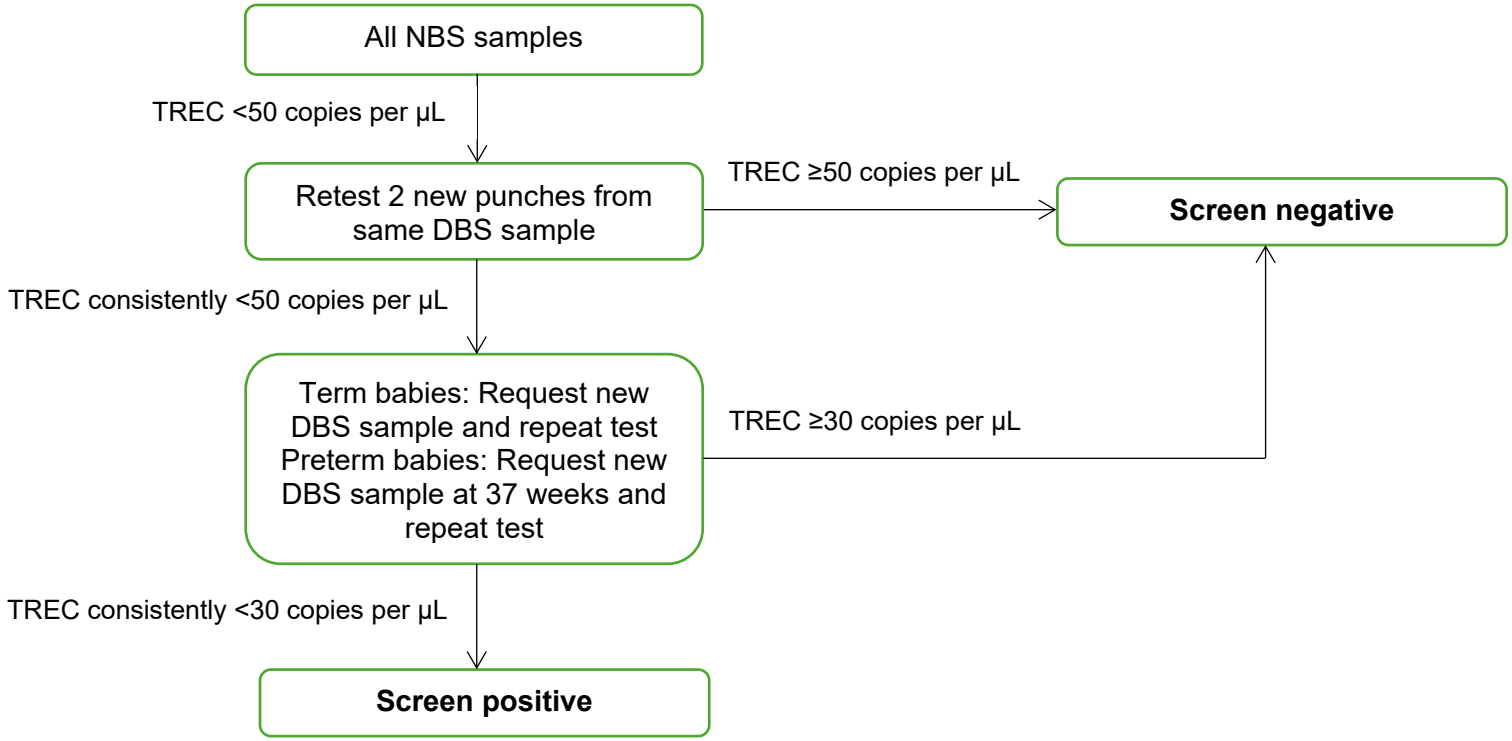
Spain (Catalonia)

Screening for SCID was added to the Catalonian NBS screening programme on 1st January 2017. The screening programme utilises TREC levels in DBS samples from heel pricks, determined using a commercial RT-PCR kit, EnLite™ Neonatal TREC kit (Perkin Elmer, Finland).[7]



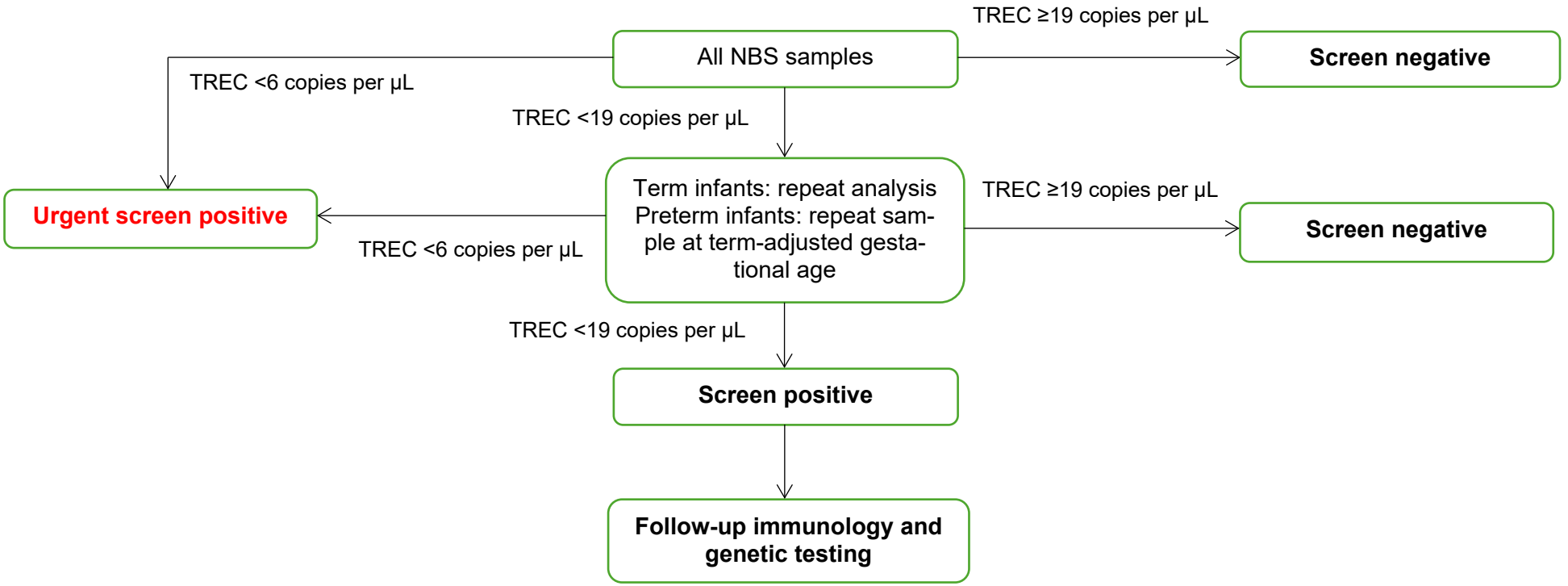
Taiwan

Screening for SCID was added to the Taiwan NBS screening programme in 2012. The screening programme utilises TREC levels in DBS samples from heel pricks, determined using RT-PCR.[25]



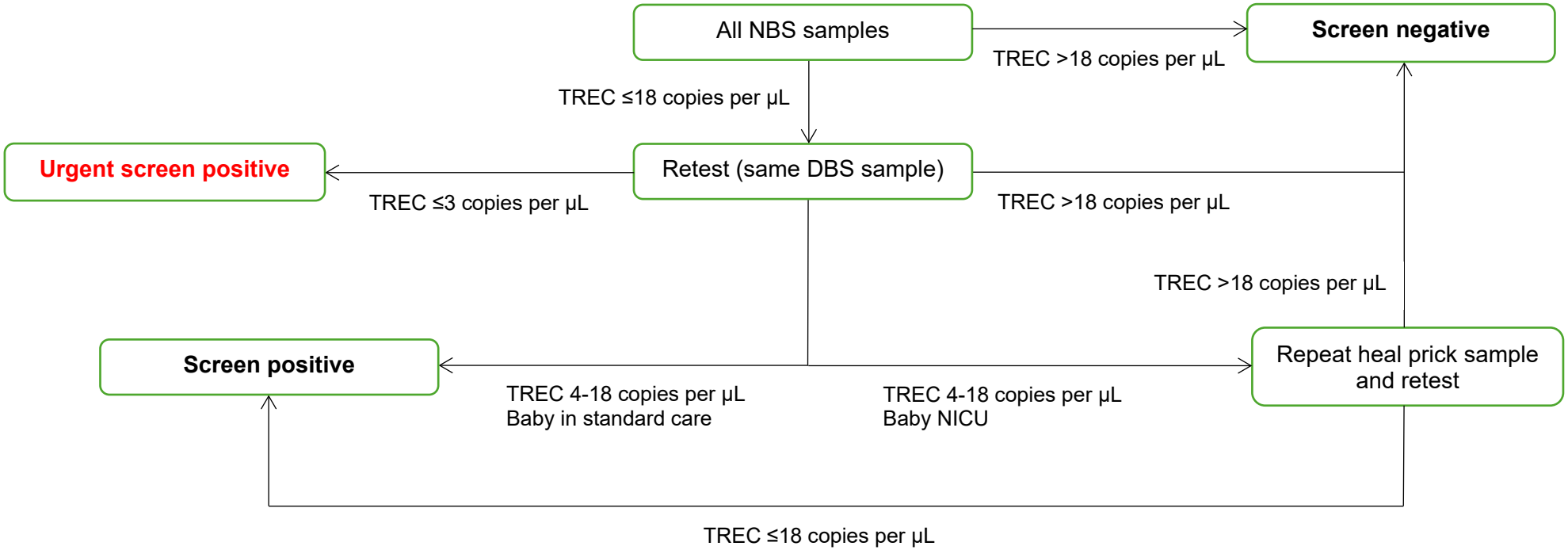
US (Arizona)

Screening for SCID was added to the Arizona NBS screening programme in 2017. The screening programme utilises TREC levels in DBS samples from heel pricks (TREC assay method not reported).[20]



US (California)

Screening for SCID was added to the California NBS screening programme in August 2010 . The screening programme utilises TREC levels in DBS samples from heel pricks, determined using a commercial RT-PCR kit, EnLite™ Neonatal TREC kit (Perkin Elmer, UK).[27]



Appendix 7 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 40.

Table 40: Reporting checklist

Section	Item	Page no.
Title and summaries		
Title Sheet	Identify the review as a UK NSC Evidence summary	Title page
Plain English summary	Plain English description of the executive summary.	10
Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review	11 to 15
Introduction and Approach		

Section	Item	Page no.
Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search. Method – briefly outline the rapid review methods used.	16 to 23
Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly(PICO, dates, language, study type, publication type, publication status etc.) To be decided a priori	23 to 28
Appraisal for quality/ risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	29
Search strategy and study selection		
Databases/ sources searched	Give details of all databases searched (including platform/ interface and coverage dates) and date of final search.	29 to 31

Section	Item	Page no.
Search strategy and results	Present the full search strategy for at least one database(usually a version of MEDLINE), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	85 to 105 (Appendix 1)
Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	23 to 24
Study level reporting of results (for each key question)		
Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	Study level reporting: 38 to 46 (Tables 3 to 5) 56 to 67 (Tables 7 to15) 76 to 82 (Tables 17 to 23) Quality assess-ment 117 to 135 (Ap-pendix 3)

Section	Item	Page no.
Additional analyses	Describe additional analyses (for example, sensitivity, specificity, PPV, etc.) carried out by the reviewer. [Remove if not performed]	112 to 115 (Appendix 3) Where possible, sensitivity, specificity, PPV and NPV were calculated
Question level synthesis		
Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and inclusion in the review, with summary reasons for exclusion	32 and 106 to 110 (Appendix 2) Searches were conducted for the whole evidence summary and not separately by question. An overall PRISMA flow chart and details of included and excluded studies are provided in Appendix 2

Section	Item	Page no.
Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four compartments should inform the reviewer's judgement on whether the criterion is "met", "not met" or "uncertain": quantity; quality; applicability and consistency.	47 to 48 54 to 55 73 to 74
Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/ risk of bias issues for each question. Have the criteria addressed been "met", "not met" or "uncertain"?	48 to 49 55 74 to 75
Review Summary		
Conclusions and implications for policy	Do findings indicate whether screening should be recommended? IS further work warranted? Are there gaps in the evidence highlighted by the review?	83 to 84
Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	83

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