UK National Screening Committee

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Evidence summary newborn screening for severe combined immunodeficiency (SCID) in the NHS Newborn Blood Spot Screening Programme

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Aim

The UK NSC is opening a public consultation following in-service evaluation (ISE) of newborn screening for severe combined immunodeficiency (SCID). We are seeking to establish whether members of the public and stakeholders support the UK NSC recommendation to continue SCID ISE.

This document provides background on the work to date on screening for SCID.

Existing recommendation

Newborn screening for SCID is not currently recommended in the UK. This recommendation was reaffirmed after a UK NSC review; completed in 2017. The 2017 evidence summary concluded that the evidence for the implementation of a screening programme for SCID looked promising, but more research was needed

before a decision could be made. 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.

Following ministerial approval of this recommendation, the Department of Health and Social Care (DHSC) and NHS England (NHSE) launched the SCID ISE in September 2021. The SCID ISE was completed in March 2024.

The 2017 evidence evaluation commissioned by the UK NSC aimed to address gaps in the evidence previously identified by the work by Lipstein 2009 and Bazian 2012. It addressed the following 3 key questions and was undertaken by the School of Health and Related Research (SCHARR), The University of Sheffield:

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

In parallel, SCHARR undertook a cost-effectiveness evaluation of screening newborns for SCID.

The 2017 review stated that SCID is a severe condition which is invariably fatal if left untreated and found that, at the time, the estimated incidence rate of SCID in the UK was 1 in 48,933.

In relation to the screening test, the 2017 evidence review found there was a candidate test for screening for SCID; measuring the number of TRECs in a dried blood spot sample (low TREC count indicating screen positive result). However, due to the low positive predictive value of the TREC test and uncertainty about the number of false positives which may be identified in the UK through a screening programme, the review concluded that UK NSC criterion 4 in relation to test accuracy was only partially met. The review stated evidence to identify a suitable cut-off for a UK screening programme was available but was limited to a small study. Therefore, a population study in the UK would provide more information on a suitable cut-off.

In relation to the key question on the effectiveness of early treatment the review concluded that HSCT is an effective treatment for SCID and that early treatment improves prognosis. However, although there were guidelines for the treatment of SCID, guidelines for the treatment of infants with a low TREC count who did not have typical SCID (for example preterm sick babies) were unclear.

The cost-effectiveness evaluation of screening newborns for SCID and modelling exercise found that a PCR-based screening strategy was estimated to cost £3.2 million per year and to have a high likelihood of being cost effective. However, some uncertainties were identified, including the cost of the test.

It was estimated that approximately 30% of SCID cases in the UK (17 cases per year at the time) would be detected through cascade testing and without the need for a screening programme.

The main benefit of screening is to find and treat babies before infections develop. The model predicted that, in a one-year birth cohort, 8 of the estimated 17 babies (almost half) would die from infections without screening and that would be reduced to around 2 of the 17 with screening. The babies found and treated before becoming infected would have the same health outcomes as those identified through cascade testing.

The model also estimated that, in the presence of a screening programme in the UK, approximately 260 families would receive false positive results. These babies would undergo diagnostic testing using flow cytometry within 2 weeks followed by an all-clear result. The evaluation also stated that of the 26 cases of non SCID T cell lymphopenia detected, approximately 7 were likely to be asymptomatic at birth.

2024 evidence summary

The aim of this evidence summary was to assess the evidence relevant to newborn screening for SCID since the previous UK NSC evaluation of the evidence in 2017.

The key questions addressed in this review were:

1. What is the test accuracy of the TREC test in population studies of screening for SCID?
2. Does HSCT in SCID cases detected in the asymptomatic period lead to improved outcomes?
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 address the above questions, the UK NSC 2024 evidence summary includes a set of vignettes describing conditions that may be detected as incidental findings from TREC based screening. The aim of these vignettes is to inform the discussion about the overall harms and benefits of screening for SCID.

This evidence summary considered research published since the completion of the previous evidence review in 2017. However, because the 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, rather than relying upon updates to previous searches.

2024 evidence summary findings

For question 1 in relation to:

- the UK NSC criterion 4, *'There should be a simple, safe, precise and validated screening test'.* The key areas of uncertainty remain those which concern how the identification of non-SCID T-cell lymphopenia (TCL), through screening, should be handled. For many non-SCID TCL conditions, treatment options remain limited and long-term prognosis unclear

- the UK NSC criterion 5, '*The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed'.* This was considered to be met by the 2017 UK NSC evidence summary. There has been no change to the evidence base, as no data are yet available from the ISE of newborn screening for SCID conducted in the NHS in England

For question 2 in relation to the UK NSC 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'. The conclusions of the 2024 UK NSC evidence summary are aligned with the conclusion of the 2017 UK NSC review.

All 3 of the new publications included in the 2024 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 all 3 studies support the conclusion that diagnosis of SCID through NBS screening is associated with improvements in survival after treatment with HSCT. However, there are still few therapy choices and an uncertain long-term prognosis for many non-SCID conditions. Evaluating the harms and benefits resulting from screen detection of non-SCID conditions remains a methodological challenge both for the non-SCID cases themselves and for gauging the balance of benefits and harms of NBS for SCID.

Question 3 was not considered in the 2017 UK NSC evidence review.

This question relates to the UK NSC criterion 6, '*The test, from sample collection to delivery of results, should be acceptable to the target population'*.

Parental support for NBS screening for SCID was generally demonstrated by the qualitative evidence included in this evidence summary. There was evidence that parents supported the reporting of incidental results because they believed that early detection of non-SCID conditions was beneficial regardless of their treatability. There was, however, a lack of evidence from parents who have had a positive result on NBS screening for SCID, particularly those who have had a positive screening result and a subsequent non-SCID diagnosis (incidental finding), as most of the evidence came from parents of healthy newborns. While there is some evidence of parental support for NBS screening for SCID and for the early identification of non-SCID conditions (incidental findings), more work may help to establish whether this criterion is met.

In-service evaluation of screening for SCID

In June 2017, the UK NSC recommended a formal ISE to address whether newborn screening for SCID would, in general, do more good than harm at reasonable cost, and whether it would be appropriate in a UK setting.

The SCID screening ISE assessed a national pathway for newborn screening, confirmatory testing, diagnosis, and care. Among 955,507 babies screened, 568 had a ‘SCID suspected’ result. Of these, 12 were diagnosed with SCID, only 2 of whom would have been identified pre-symptomatically without screening. The overall positive predictive value (PPV) for SCID was 2%, which modelling suggests could rise to 11% depending on the method of the test. Additionally, the majority of screen positive babies had normal flow cytometry results (false positives) while 56 babies were identified with non-transient, non-SCID T-cell lymphopenia. The clinical, logistic and qualitative consequences of introducing TREC screening into the newborn screening pathway are described in the consultation package.

Assessing the cost-effectiveness of screening for SCID in the newborn blood spot screening programme: NHS SCID Screening Evaluation in England

This modelling study evaluated the cost-effectiveness of newborn screening for SCID in the UK. When assessed independently, SCID screening yields an incremental cost-effectiveness ratio (ICER) of £80,000–£90,000 per QALY gained. The 95% confidence interval for net monetary benefit is entirely negative, indicating it does not meet current usually accepted thresholds. Cost effectiveness is highly sensitive to SCID birth prevalence, which was lower during the evaluation period than modelled averages, and varies geographically across the UK, with Scotland, Wales and Northern Ireland having lower prevalence than England. However, when SCID screening is integrated in the model if spinal muscular atrophy (SMA) screening was in place and using shared laboratory processes, cost-effectiveness improves significantly, falling below £10,000 per QALY gained.

Overall, SCID screening may be economically viable when combined with SMA screening, but standalone implementation remains above current NICE and UK Government thresholds. Therefore, it is not cost-effective under current conditions.

UK NSC recommendation

The UK NSC is recommending that the ISE for SCID continues.

This will allow more time to consider and address the recommendations from the ISE report. For example, to:

- offer screening for both SCID and SMA on the same testing platform where appropriate and feasible
- ensure the SCID tests are robust and sustainable in this context
- assess whether there are follow-on tests (for example genetic tests) which can improve the accuracy of the SCID screening process
- provide an opportunity to gather 5-year follow-up information on the impact of positive screening results on children
- evaluate the cost, feasibility, and accuracy of combining screening for SCID and SMA together.