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

Date: March 2026

Contents

Aim

This document provides the background information and an overview of the consultation comments related to the UK NSC public consultation on the UK NSC evidence summary for newborn screening for severe combined immunodeficiency (SCID) and the in-service evaluation (ISE) in the NHS Newborn Blood Spot screening programme.

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.

2025 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.

2025 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.

Action

The UK NSC is asked to note the consultation responses and approve the recommendation.

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.

Consultation

A 3-month public consultation (8 August to 27 October 2025) was hosted on the UK NSC website. Direct emails were sent to 18 stakeholders. (Annex A)

Comments were received from the following stakeholders:

a. 6 members of the public
b. Matthew Babirecki, Consultant paediatrician, Airedale NHS FT
c. Tomaz Garcez, Consultant Immunologist
d. Christo Tsilifis, Specialty Training Doctor in Paediatrics; NIHR Academic Clinical Fellow in Paediatric Immunology & HSCT, Great North Children's Hospital, Newcastle upon Tyne
e. Joanna Lowry, Specialist Nurse, Immunisation Education
f. Ruth Radcliffe, Consultant Paediatrician, University Hospitals of Leicester

g. Andrew Gennery, Paediatric Immunologist, Great North Children's Hospital/Newcastle University
h. Ben Shillitoe, Consultant in Paediatric Immunology and Infectious Diseases, Sheffield Children's Hospital
i. Paul Torpiano, National representative for immunology, British Paediatric Allergy, Immunity and Infection Group
j. Beverly Hird, Director of Manchester Newborn Screening Laboratory, Manchester University NHS Foundation Trust
k. Michelle Mills, KS NBS Laboratory Manager, State of Kansas Department of Health and Environment
l. Paul Torpiano, Consultant in Paediatric Immunology, Organisation: Immunology Consultant Team, Immunology Department, Directorate for Blood, Cells and Cancer, Great Ormond Street Hospital for Children NHS
m. Sue Dimmock, Joint-Chair, UK Primary Immune-deficiency Patient Support
n. Monica Thakar, MD, Pediatric Immune Deficiency Treatment Consortium
o. Susan Walsh, CEO, Immunodeficiency UK
p. Patricia Roberts, Director for Newborn Screening, ArchAngel MLD Trust
q. Rosanna Flury, on behalf of the British Society for Immunology Clinical Immunology Professional Network
r. Dani Bancroft, on behalf of Genetic Alliance UK

The consultation comments received are presented below in Annex B.

Summary of comments by topic and responses

Families and PPV responses to the consultation

Comments

Lived impact of SCID

The consultation highlighted the profound impact of families' lived experiences in underscoring the critical importance of early diagnosis of SCID through newborn screening. Many parents attributed the survival of their children to timely detection, which enabled access to life saving interventions such as stem cell transplantation.

Impact of delayed diagnosis

In contrast, accounts of delayed diagnosis revealed the serious consequences of prolonged illness, delayed diagnosis, and irreversible complications, including chronic conditions. Families described the significant emotional trauma associated with these delays, as well as the wider social and financial burdens of caring for affected children, ranging from isolation and disrupted family bonding to loss of income and extended hospital stays.

Support for screening

Overall, there was strong and consistent support for the introduction of national SCID screening. Stakeholders emphasised the need to extend the current interim service evaluation (ISE) to children born outside ISE areas, in order to reduce inequities in access. Many respondents urged the UK NSC to recommend a national newborn screening programme for SCID, framing this as an ethical responsibility to ensure timely diagnosis and equitable care for all children.

Although they would prefer a national roll-out, some stakeholders support continuing the SCID ISE alongside an ISE of SMA screening, but they warn that this might perpetuate inequity.

Stakeholders also drew attention to international examples where newborn screening for SCID is already established, reinforcing the benefits of early identification.

Response

The UK NSC and NHS England acknowledge the profound impact SCID has on affected individuals and their families. The lived experiences of children and families are a vital consideration in evaluating the evidence on the potential benefits and harms of screening.

The personal accounts submitted in response to this consultation are an important and powerful statement of the profound effect SCID has on individuals and their families. The UK NSC and NHS England wish to acknowledge the contribution of the perspective these responses provide alongside the scientific evidence considered.

The balance of benefits vs harms

The UK NSC only recommends the introduction of a national population screening programme if evidence demonstrates that it will provide more benefit than harm at affordable cost for the eligible population as a whole. The committee must consider this balance of benefits and harms across the entire population of approximately 600,000 newborns born in the UK each year, not just those affected by a condition.

Potential harms, of screening can include overdiagnosis, overtreatment, false positive results, false reassurance, uncertain findings, or complications.

Using UK-specific evidence

The UK NSC's evidence review process systematically evaluates international peer-reviewed primary evidence alongside health economic modelling. However, because this evidence is interpreted through the lens of UK population health and NHS resources, findings from other countries may not translate directly into UK practice. This is due to the unique structures, care pathways, and service delivery models within the NHS. Health outcomes, disease prevalence, service configurations, and risk factors also vary between countries. Therefore, it is important when possible that the committee's recommendations are grounded in UK-specific evidence and health economic analyses. This approach ensures screening programmes are tailored to the UK population rather than extrapolated from contexts that may not apply. Using UK-specific data makes recommendations robust, defensible, implementable, and an efficient use of NHS resources.

The UK NSC's assessment of the effectiveness and cost of different health interventions ensures that its recommendations reflect not only economic impact and value for money, but also the suitability for the UK healthcare system and the effectiveness of screening programmes within the UK population.

The data collected during in-service evaluation (ISE) work helps determine whether a screening programme would be evaluated whether both clinically effective and economically sustainable within the NHS. The health economic evaluation of SCID screening, based on data from the ISE, does not support the introduction of a national screening programme at this stage. As a result, the UK NSC is unable to recommend extending the ISE to a wider population. However, it is recommending that the ISE should continue, as emerging evidence indicates that introducing the

screening programme alongside newborn screening for SMA could improve its cost effectiveness and strengthen the case for future implementation.

Comment

Extending the ISE

Some stakeholders thought that extending the ISE would only delay a positive recommendation for SCID screening and therefore is unwarranted. Stakeholders suggested that as SCID screening, when combined with SMA, is likely to be cost-effective, failing to implement it equally across the UK will create serious equity issues. Other countries have implemented SCID and SMA screening much earlier, leaving UK newborns at a disadvantage. The UK NSC is urged to prioritise combined SCID and SMA screening as an urgent equity matter, minimise uneven roll-out, and focus on nationwide implementation rather than further postponement.

Response

The UK NSC recognises that early detection of SCID is clinically effective. However, cost-effectiveness remains a key concern.

The committee therefore had 3 options for its recommendation:

- to stop the ISE of newborn screening for SCID due to lack of cost-effectiveness. This was not considered an appropriate option because the option of combining screening for SMA is still under evaluation
- continue the ISE to gather more data. The primary rationale for continuing the ISE is to address existing uncertainties, such as case numbers and characteristics, and to refine protocols to minimise false positive results. This will enable a better understanding of the implications of national implementation and inform how to optimise that process, and
- to roll out a national programme deemed not to be cost-effective. This would be considered untenable without the inclusion of SMA, which needs to be fully evaluated before being implemented.

The UK NSC believes that continuing the ISE until more information is available is the best way forward to enable the collection of further evidence and to understand the implication of implementing screening for SCID alongside screening for SMA.

Clinicians and experts' responses to the consultation

In general, there was a strong consensus between clinicians, experts in the field and support groups that SCID newborn screening improves survival and outcomes. They also emphasised that early Hematopoietic Stem Cell Transplantation (HSCT) (before infection) leads to better prognosis.

Although there is no UK-specific evidence supporting cost-effectiveness, there was no support for suspending the ISE for newborn screening within the SCID programme. However, there was strong support for continuing the ISE and integrating SCID and SMA screening.

There was also support for implementing reflex genomics to reduce false positive results in the NBS SCID screening programme.

Additionally, stakeholders supported incorporating findings from the BCG programme into reviews and planning for the NBS SCID programme.

Finally, there was agreement on implementing clinical protocols for managing non-SCID T-cell lymphopenia to ensure consistent and effective care.

Comment

'*Postcode lottery'' of screening provision*

Concerns were raised about postcode lottery: babies in non-ISE areas facing delayed diagnosis and worse outcomes.

Response

The current evaluation does not support introducing a national screening programme at this time. Nevertheless, the UK NSC advises that the ISE should continue in its present form, as there is encouraging evidence that combining it with newborn screening for SMA could be highly cost effective. We acknowledge that this may lead to unequal access to treatment for some individuals, but since the programme remains under evaluation and full implementation is not yet supported by evidence, some inequities are inevitable, as with any research trial.

Comment

Impact of changes to BCG vaccination programme

Concerns were raised that moving the timing of Neonatal Bacillus Calmette-Guerin (BCG) vaccination to around 28 days after birth, to avoid vaccinating infants who might later be diagnosed with SCID, could reduce uptake. Stakeholders asked whether this has been assessed during the ISE.

Response

This issue is addressed briefly in the main body of the ISE report and in greater detail in Appendix 12. Reliable data from before the establishment of the ISE are limited. However, the available evidence indicates that uptake by 12 months has increased (see Figure 2, Appendix 12), though vaccinations are now being administered later than was previously the case (see Figure 3, Appendix 12).

Comment

Programme implementation concerns

Some stakeholders raised concerns about the operational and logistical issues related to the implementation of the entire screening programme pathway and the funding and resources involved. They suggested that should national implementation proceed, additional funding and resources will be essential. This is particularly important for smaller centres, where the staffing establishment means they are disproportionally affected. Timely delivery of care for screen positive babies, as required by the programme, cannot be achieved without targeted support. They also expressed concern that extending the current ISE for SCID screening will lead to an interim service that is unstructured and underfunded.

Response

The UK NSC acknowledges the concerns raised regarding the operational and logistical challenges of implementing a national screening programme, particularly in relation to funding and resources. We recognise that smaller centres may be disproportionately affected due to limited staffing capacity, and that timely delivery of care cannot be achieved without appropriate support. Should national implementation be considered in the future, the committee agrees that these operational and resource issues will need to be carefully addressed. However, this

fall outside the remit of the UK NSC's recommendation, which is focused on the evidence of benefits and harms of screening.

Extending the ISE will enable further revision of pathways to reduce false positive rates and clarify management protocols for children with a screen positive result.

Comment

Incidental findings

Stakeholders noted that although newborn screening for SCID can sometimes identify conditions beyond the target disorder, early detection may enable treatments or support that improve e of life for these conditions, which might otherwise remain undiagnosed. Therefore, the UK NSC's concerns about incidental findings may be overly cautious and should not necessarily be viewed as a negative factor in the implementation of the screening programme.

Response

Incidental findings in newborn screening for SCID present significant challenges. The test 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) that an individual has. Below a certain number, the test is considered to be an abnormal (or 'positive') test result. 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. Therefore, the screening tests used in the SCID screening programme may unintentionally detect other conditions in newborns, this must be considered carefully. Although early detection of such conditions could be seen as beneficial this may not always lead to improved outcomes for the baby, particularly when the condition is untreatable or has limited clinical significance. In such cases, the information may offer little practical benefit while introducing unnecessary anxiety and emotional burden for families. Parents may experience distress when told their child has a condition that cannot be treated, particularly when the significance of the finding is uncertain. This can lead to stigma, altered family dynamics, and long term anxiety.

Furthermore, managing these incidental findings can place additional strain on healthcare resources and complicate care pathways. Even untreatable incidental findings require immunology input, genetic counselling, and family support. Yet these cases are often excluded from cost evaluations, underestimating the true workload and resource impact.

For these reasons, policy decisions should weigh the potential advantages of broader detection against the ethical, psychological, and operational implications, ensuring that screening programmes remain focused on conditions where early intervention provides clear and meaningful benefit.

Comment

Clear referral pathway

There was a general support for a clearer referral pathway.

Response

We agree with the recommendation regarding the need for national standardisation of follow up and management practices. This is particularly important for the cohort of infants identified with idiopathic T cell lymphopaenia through SCID NBS, where current approaches vary between centres and generate significant additional clinical workload. We also emphasise that standardisation should extend to the management of babies who screen positive but do not survive to undergo confirmatory flow cytometry.

National guidance should therefore include clear timings and thresholds for antibiotic prophylaxis, BCG administration, and genomic investigations, as well as recognition of infants who die prior to confirmatory. These cases still require immunology input and family support, and their inclusion is essential to provide a comprehensive and accurate picture of the resource impact.

Work on these issues will continue during the ISE.

Cost Effectiveness and Modelling Concerns:

Comment

Accuracy of Cost Effectiveness Studies

Multiple comments highlight the inherent difficulties in accurately modelling cost effectiveness for rare diseases like SCID. The low incidence and variability in outcomes make reliable estimates challenging, and small changes in assumptions can lead to vastly different results. Therefore, they asked for caution in interpreting these findings.

Response

The evidence base for SCID screening has improved significantly, with comprehensive UK-specific data now available from both retrospective and prospective studies. The economic model uses the best available UK data, including a 10-year retrospective cohort, which provides robust estimates for treatment effectiveness and survival.

Comment

Survival Rate Estimates

The cost effectiveness model is critiqued for overestimating long-term survival rates of symptomatic (non-screened) SCID babies. It points out that cited studies only include patients who survived to receive treatment, excluding those who died before diagnosis or treatment, thus inflating survival rates used in the model.

Response

The survival rates for symptomatically diagnosed SCID children in the cost effectiveness model are derived from a 10-year retrospective UK cohort, which includes up to 14 years of follow-up. This cohort is consecutive and complete, making it the best available source for treatment effectiveness in the UK context.

It is acknowledged that survival observed during the recent evaluation period was lower than in the retrospective cohort. However, the sample sizes differ significantly: 109 SCID babies in the retrospective cohort versus only 7 in the evaluation period. . The respective confidence intervals for survival estimates are (61%, 78%) for the retrospective data and (4%, 64%) for the evaluation period. Clinical advice also

indicated a cluster of severe cases during the evaluation, and the Covid-19 pandemic may have affected the generalisability of the ISE outcomes.

The SCHARR model does not use survival rates from the Thakar or Hardin studies directly; these are cited for background only. The model uses data from Hardin et al. solely to inform annual survival estimates for ages over 10 years. Published Kaplan-Meier survival graphs are used to generate simulated SCID datasets from and moderating these with all-cause mortality data from the ONS, in line with NICE recommendations.

For mortality up to 10 years of age, including the period before definitive treatment (mainly HSCT), the model relies on UK-specific retrospective data and the SCID evaluation. While estimates for ages over 10 are necessarily based on older treatment cohorts and may be biased under current management techniques, this approach improves upon previous models that simply used all-cause mortality beyond early years.

Therefore, the model prioritises robust, UK-specific data for survival up to age 10, and uses international data only for older ages, following NICE guidance. This ensures that survival estimates are as accurate and relevant as possible for the UK population.

Similarly, in relation to pre-transplantation infections, the Lankester study results are not used in the economic model. The Lankester results are referred to in the SCHARR economics report for background, context and completeness. Specifically, it is not intended to imply evidence against benefits from early transplantation.

It may be worth noting, however, that emerging evidence on the impact of early infections on survival and transplant success suggests that concurrent infections may be a more important driver of outcomes than prior infections

Comment

Bias in Data Sources

Concerns are raised about the retrospective cohort data from specialist centres (GOSH/NUTH), which may not represent the broader population due to selection bias. It is suggested these centres attract families with resources and prior

knowledge, leading to higher survival rates than would be seen in the general population.

Response

The SCID Model is designed to address potential bias by including functionality to account for undiagnosed SCID deaths in both arms of the model. This ensures that, if screening were to identify additional cases, these would be captured in the analysis.

A thorough investigation of child mortality records within the English healthcare system (including Hospital Episode Statistics (HES) and the Child Mortality Database) was conducted for the period of the evaluation. This review did not find evidence of children with SCID being missed.

Additionally, there was no indication of an increased birth prevalence of SCID being revealed by screening in the areas covered during the evaluation. This suggests that the retrospective cohort data are representative of the population eligible for screening.

All babies diagnosed with SCID in England would be referred to or discussed with specialists at NUTH/GOSH.

Importantly, the retrospective cohort included only patients who would have been eligible for screening in the UK. For example, international patients who have sought treatment at GOSH/Newcastle have been excluded.

Therefore, socioeconomic factors such as wealth and ability to travel are not relevant in the UK NHS setting. These factors highlight the importance of having locally generated evidence rather than relying on generalisation between international settings.

Clinical Effectiveness and Patient Outcomes:

Comment

Clinical Benefits of Screening

The document emphasises the marked clinical effectiveness of SCID newborn screening, with significantly higher survival rates for screened babies compared to those diagnosed clinically. Early diagnosis also benefits patients with related immune deficiencies, reducing long-term health burdens.

Response

The SCHARR model uses long-term UK cohort data to estimate outcomes for clinically diagnosed SCID cases, preferring this over the limited evaluation period data. While the clinical effectiveness of screening is clear (e.g., 92% survival for screened babies), long-term outcomes for non-SCID T-cell lymphopenia cases are not included due to lack of comparative data

Comment

Quality of Life and Economic Impact

There is a strong argument that the full economic and psychological impact of SCID, especially on families, is underestimated. The trauma, mental health issues, and hidden costs associated with late diagnosis and bereavement are not fully captured in current analyses.

Response

The model is the first to explicitly assess the negative parental quality of life impacts of child bereavement avoided by screening. The model also includes an assessment of the negative parental impact of receiving a false positive result. However, sample sizes in the parallel SCID outcomes research study quality of life studies were insufficient to identify differences between screen positive groups. The economic analysis focuses on NHS costs and outcomes, so family costs are not included.

Comment

Parental HRQoL Impacts from Bereavement

While the SCHARR report does attempt to quantify parental bereavement impacts, there is uncertainty about whether it fully captures the depth and complexity of the experience for families affected by SCID, particularly those excluded from screening.

The stakeholders advocates for more in-depth research into these impacts, to ensure they are given appropriate weight in future evaluations.

Response

This is less an economic issue but an ethical impact of ISE. However, the economic model includes an assessment of the avoided bereavement impacts for parents.

Comment

Methodological and Policy

QALY Threshold and Policy Decisions: There is criticism of the static QALY threshold (£30k) used for evaluating screening programmes, noting that it has not kept pace with rising costs and advances in treatment. The document questions whether this threshold is a fair barrier to implementing SCID screening.

Response

The definition of the economic threshold is ultimately a matter of policy and it is outside the remit of this work. The consultee rightly highlights a potential challenge arising from the application of different thresholds for rare disease treatments. This issue becomes particularly significant when considering population-level public health interventions such as screening.

The modelling, however, indicates that the cost of implementing the screening test represents the largest component of the overall screening expenditure. Notably, the net treatment costs are actually cost-saving in the baseline analysis, despite the high upfront cost of definitive treatment.

Comment

Impact of Birth Rate Trends

The relevance of falling birth rates to cost effectiveness is questioned, with a suggestion that this should not be a decisive factor in screening policy.

Response

The health economic report does not consider trends in birth rate over time. However, the potential impacts on the economics of SCID screening are not so much from falling birth rates as from the changes in the birth prevalence of SCID.

Operational and Implementation Issues

Comment

Screening Protocol Improvements

Suggestions are made for improving cost effectiveness through operational changes, such as tighter diagnostic thresholds, adopting a single national platform, and sharing infrastructure costs with other screening programmes.

Response

The costs of screening in the model have been based upon projected normal screening costs informed by the evaluation, rather than directly upon the evaluation. For example, the economic analysis focuses on a single diagnostic platform and laboratory staffing levels within the evaluation were adjusted to an expected normal service level.

The potential to improve the screening process is recognised. Whilst the model suggests these are unlikely to overturn the economic results of themselves, it is important to ensure that data collection is built into any screening system going forward to enable such process optimisation.

Epidemiological Complexity

Comment

Variability in Prevalence

The document discusses the challenges of extrapolating short-term evaluation data to long-term service planning, given the random variability in SCID prevalence year-on-year and the emergence of novel genetic defects.

Response

The model uses birth prevalence data from the 10-year retrospective cohort, recognising that the evaluation period's low prevalence is within historical variation. The low prevalence observed during the evaluation is within the range seen over the retrospective period. The model also notes that the Covid-19 pandemic may have affected birth prevalence, management, and outcomes during the evaluation. For both prevalence and outcomes, the model relies on data from the retrospective cohort as well as the evaluation period.

Annex A: List of Organisations Contacted

1. ArchAngel MLD Trust
2. Ataxia Telangiectasia Society
3. British Association of Perinatal Medicine
4. British Paediatric Allergy, Immunology and Infection Group
5. British Society for Immunology
6. CGD Society
7. Genetic Alliance UK
8. INGID - International Nursing Group for Immunodeficiencies
9. IPOPI - International Patient Organisation for Primary Immunodeficiencies
10. Metabolic Support UK
11. Primary Immunodeficiency UK
12. Royal College of General Practitioners
13. Royal College of Paediatrics and Child Health
14. Royal College of Physicians
15. Royal College of Physicians and Surgeons of Glasgow
16. Royal College of Physicians of Edinburgh
17. UK Primary Immune-deficiency Patient Support
18. UK Primary Immunodeficiency Network

UK National Screening Committee

Annex B: Consultation Responses

Note: Personally identifiable information has been redacted from certain comments, where individuals have chosen not to have personal details made public.

Name: Elizabeth Ann Gardner
Email: XXXX XXXX
Notify: True
Condition: SCID
Affected Comment:
Our grandson was born on XXXX XXXX in XXXX XXXX Spain. At 3 days old, thanks to the heel prick test which includes screening for SCID routinely in Catalonia he was diagnosed with X-linked SCID. He was immediately put on a raft of medication to keep him healthy and isolated at home. At 3 months old he had a course of chemotherapy and then a stem cell transplant from an umbilical cord donation during a 6 month stay in an isolation chamber in hospital with his XXXX XXXX. All in Spain. There have been many ups and downs – some skin reactions to the transplant requiring immunosuppressants which he still takes in a low dose, lymphodaema causing a very swollen left leg and other minor issues. His growth is also stunted due to the steroids following the transplant. There have been countless trips to hospital and several to A and E when something unexpected occurred – calling ahead and asking for an isolation room.
At XXXX XXXX months old he is now happy, healthy and thriving and is being weaned off the medication. He recently overcame COVID spending XXXX XXXX more days in hospital being monitored and on IV antibiotics – this virus would have more than likely not been survivable without the treatments. He is due to start nursery school in XXXX XXXX
It has been a tough and traumatic (almost) XXXX XXXX years for all the family but particularly his parents – XXXX XXXX. Thanks to the working-from home approach and the fact that he was their first child they could

spend most of the time in their flat and XXXX XXXX could work from home. We had planned to visit from the UK the week after his birth but had to stand outside the apartment and wave. It was April the following year when he was XXXX XXXX months old before we could be in the same room and hold him although we wore surgical mala the whole time terrified we would pass a cold or other virus on to him.

Our wider family are just meeting him now as he approaches his XXXX XXXX birthday as he has finally been given the all-clear to fly from Spain to the UK.

Our XXXX XXXX have put their lives on hold for this last XXXX XXXX years focusing on keeping their son well. But what a positive outcome. Without the early diagnosis I feel this could have been a very different outcome. I am so relieved our XXXX XXXX and XXXX XXXX Spanish XXXX XXXX chose to settle in XXXX XXXX. If he had been born where we live he would not have been screened and diagnosed. He would have very likely become seriously ill with no immune resources to fight off infection and by the time diagnosis was managed too sick to survive the treatment. A harrowing thought which has caused me to have sleepless nights. I feel it is crucial that SCID be screened for routinely in the UK.

Evidence Comment:

As stated above I understand that early screening has proved cost effective in a pilot scheme. Costs of screening and subsequent treatment of affected babies surely outweighs the costs of keeping very poorly children alive, late diagnosis and attempts to treat very sick children and babies – never mind the distress and heartbreak for the families. It also means that knowledge of the treatment of SCID including gene therapies is advancing all the time potentially in the future eliminating some types of SCID.

Discussion comment:

The UK has been sadly lagging behind many other first world countries with our screening programmes – few conditions are screened for here compared with many European countries and the US. This is surely unacceptable.

Recommendation comment:

I feel screening should be recommended based on our own experience with our grandson and the research I have done into the Great North Children's Hospital and Great Ormond Street Hospital where SCID babies are treated in the UK. I have read some heartbreaking stories about babies with SCID who died because of late diagnosis or no diagnosis and only the knowledge in hindsight that that is what must have been the cause of death. We have the means to rectify this awful situation using a quick, simple test. We now require the will.

Alternatives comment:

I don't feel that there is a realistic effective alternative.

Name: Kay Hopson
Email: xxxx xxxx
Notify: True
Condition: SCID

Affected Comment:

New born babies should be screened.
My xxxx xxxx has SCID.. it wasn't diagnosed until xxxx xxxx was over a year old. Because of this late diagnosis xxxx xxxx has suffered considerably and is now on a cocktail of medication to keep xxxx xxxx alive.

Recommendation comment:

Yes it should recommended.
Because of my reasons above.

Name: Kayleigh Davies
Email: xxxx xxxx
Notify: True
Condition: SCID

Affected Comment:

My xxxx xxxx was disavowed with RAG1 SCID in xxxx xxxx.

Recommendation comment:

Screening absolutely should be recommended.My xxxx xxxx was diagnosed with RAG1 SCID in xxxx xxxx at the age of 23 months. xxxx xxxx had endured almost xxxx xxxx of very poor health, multiple hospital admissions and surgeries. xxxx xxxx was misdiagnosed with intestinal lymphangiectasia after developing protein losing enteropathy. xxxx xxxx went on to develop haemolytic anaemia and it was only then that xxxx xxxx was transferred to xxxx xxxx for further investigation of an immune deficiency. xxxx xxxx suffered massively in that xxxx xxxx. As a family we suffered unimaginable pain and fear as we came so close to our losing our baby on multiple occasions. The lack of knowledge and understanding of xxxx xxxx actual disease meant that I was treated as a neurotic mother and it was suggested I had post natal depression when in fact, had xxxx xxxx been diagnosed at birth xxxx xxxx would have had treatment and understanding from the beginning of xxxx xxxx life. xxxx xxxx had a bone marrow transplant in xxxx xxxx. xxxx xxxx has suffered multiple complications since and now lives with Bronchiolitis Obliterans which was possibly caused by the year of misdiagnosis and multiple chest infections. At the age of xxxx xxxx still takes up to 20 medications a day, has regular admissions to hospital and has daily chest physiotherapy. This is a dramatic difference to children who have the same disease as xxxx xxxx but live in countries where they test and treat at birth. Most children with xxxx xxxx disease go on to live full, almost normal lives if treated at birth. xxxx xxxx has not had that privilege. xxxx xxxx will suffer for the rest of xxxx xxxx life because of late diagnosis. xxxx xxxx care, undoubtedly has cost the NHS hundreds of thousands of pounds, if not more. It will continue to do so for the rest of xxxx xxxx life, however long that may be. You see this is another thing we aren’t

promised due to late diagnosis- we aren't promised a long life with XXXX XXXX

Alternatives comment:

Far better training to all paediatric doctors of the symptoms and concerns of primary immune deficiency.

Other comments:

A protocol that recommends children who present at hospital multiple times for infections should be TIGER panel tested to rule out immune deficiency.

Name: XXXX XXXX
Email: XXXX XXXX
Notify: False
Condition: SCID

Affected Comment:

My friends son suffers daily with SCID. He was diagnosed late and struggles with daily life. His condition is limiting meaning he cannot enjoy his childhood the same as other children.

Recommendation comment:

There is a huge delay in a diagnosis when the screening isn't issued to newborns. It causes the child to suffer daily which could be prevented if the condition is found early. The screening could save lives, improve the quality of life and save a lifetime of pain and suffering for the child and family.

Name: Matthew Babirecki
Email: XXXX XXXX
Organisation: XXXX XXXX

Role: Consultant paediatrician
Publish submitter's name: True
Publish Organisation name: False
Condition: SCID
As the assessment led to changes in the BCG programme there were concerns that BCG uptake would be lower. Has this been assessed? We were particularly concerned about this in XXXX XXXX as out babies have not been part of the SCID programme.

Name: Peter William O'Donnell
Email: xxxx xxxx
Notify: True
Condition: SCID

Affected Comment:

This condition has severely affected all family members, the stress of the struggle to get a diagnosis, eventually getting it and then trying different treatments, all the while my xxxx xxxx losing weight and xxxx xxxx hair. Not knowing whether xxxx xxxx would survive and daily ups and downs, my xxxx xxxx spending a big part of xxxx xxxx life in the hospital with xxxx xxxx. xxxx xxxx siblings getting less family time. xxxx xxxx was a donor with all that entails. Any parent or grandparent would not hesitate to recommend any early diagnosis available

Recommendation comment:

Definitely recommended for the above reasons. The stress on families. To those reading this just think if it was family member of yours and decide what would you do.

Alternatives comment:

Give the parents or responsible person, free parking a blue badge and ULEZ refund on application

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Name: Tomaz Garcez
Email: xxxx xxxx
Organisation:
Role: xxxx xxxx
Publish submitter's name: True
Publish Organisation name: False

Condition: SCID

General comments only. I would support new born screening of SCID mainly due to the impact this condition has if not detected early and the fact that it can be cured if detected early.

Name: Christo Tsilifis
Email: xxxx xxxx
Organisation: xxxx xxxx
Role: Specialty Training Doctor in Paediatrics xxxx xxxx
Publish submitter's name: True
Publish Organisation name: False

Condition: SCID

Newborn screening for SCID via TRECs has been hailed as pivotal to improving the survival and outcome of this rare immunodeficiency which carries a high mortality rate. Outcomes are demonstrably worse for patients diagnosed clinically, rather than by screening (in other countries that have piloted and adopted the programme) or by family history. Yet, family history can only aid us in diagnosing ~1/5 patients. It is disappointing that the current evaluation shows SCID screening as not being cost-effective, given that we are by no means the first country to evaluate this and that other countries have found it cost-effective enough to implement (albeit with differing health systems and funding).

As a clinician working on a stem cell transplant unit that sees these patients, it has been great seeing babies referred in without the

stigmata of chronic and persistent viral infection, failure to thrive, or lung damage that typically denote a SCID diagnosis. In the absence of SCID screening being adopted in England fully, it is welcome that screening will continue in ISE areas however I am concerned this deepens inequity. Babies born with SCID in “the right area” will, by virtue of this postcode lottery, be given the best chance of survival as it is clear from published data that younger age, screening, and no infection all positively influence HSCT outcomes. However, babies born a few miles away outside of the ISEs will have to wait until they present with significant morbidity before diagnosis.

We wish to provide the best possible outcome for all patients that are seen by our service. SCID screening would support this goal, and I hope that further review of this consultation and of the results of SMA screening pilots will influence the decision of the screening committee.

Name: XXXX XXXX
Email: XXXX XXXX
Organisation:
Role: Specialist Nurse
Publish submitter’s name: False
Publish Organisation name: False

Condition: SCID

I have followed the introduction of SCID screening with interest. I do not have a personal reason for doing so, purely professional. I am keen to see more research into why abnormalities were found in the results and wonder if other conditions may be identified early through this screening.

It is amazing to have a screening programme which has minimal invasiveness but for the 10 babies who were positive to SCID, allows them a potential future. I appreciate this is an expensive programme for only a few children, but hopefully it also allows further research into SCID and other immunological conditions if babies with SCID are diagnosed early.

Name: XXXX XXXX
Email: XXXX XXXX
Organisation: University Hospitals of Leicester
Role: Consultant Paediatrician
Publish submitter's name: False
Publish Organisation name: True

Condition: SCID

SCID Newborn Screening Programme: Response and Key Considerations

We welcome the findings of the current evaluation, which reinforce previous evidence of the clinical benefits of Severe Combined Immunodeficiency (SCID) Newborn Screening (NBS). In light of this, we offer the following observations for consideration ahead of any decision regarding wider national implementation.

1. Costing Model and Financial Implications
   We find the costing model presented to be broadly fair and reflective of current expenditure, and we welcome the report's recognition of the burden placed on local centres. However, concerns remain regarding the financial and logistical implications for non-HSCT centres, which are likely to be most impacted by national rollout.

Currently, it is unclear whether future pathways would continue to require all "SCID-suspected" infants to be referred to regional centres, (which could be many hours travel for a family with a young baby) or whether local hospitals will be resourced to manage aspects of care more directly.

A UK-wide SCID NBS programme would require increased support for local centres. For example, the management of premature infants is already a challenge and would be further amplified if more district general hospitals (Level 1/2 units) are involved in the pathway.

While SCID NBS is not yet deemed cost-effective at a national level, it is important to recognise that the primary financial benefits—through avoidance of severe infections prior to HSCT—are reaped within HSCT centres. Conversely, the screening programme causes increased clinical activity in local centres, without corresponding resource allocation. The on-going evaluation continues to place substantial operational pressure on medical, nursing, and administrative teams within non-HSCT centres. Should national implementation proceed, additional funding and resources will be essential. This is particularly important for smaller centres, where the staffing establishment means they are disproportionally affected. Timely delivery of care, as required by the programme, cannot be achieved without targeted support. A future funding model must account for this imbalance to ensure equity and sustainability.

1. Standardisation of Follow-Up for Idiopathic T-cell Lymphopaenia
   The identification of incidental idiopathic T-cell lymphopaenia cases through SCID NBS has introduced a new patient cohort requiring follow-up, generating significant additional clinical workload. Current follow-up and management practices may vary

between centres, and we strongly agree with the recommendation for development of national guidance to ensure consistency. Standardisation should include timings and thresholds for:

2. Antibiotic prophylaxis
3. BCG administration
4. Genomic investigations
5. Inclusion of babies who die in screening costs
   We note that the current cost evaluation does not account for SCID-suspected infants who die prior to confirmatory flow cytometry. These cases still require immunology input and family support, and should be reflected in future cost assessments to provide an accurate, comprehensive picture of the resource impact.
6. Clarification on Duration of Evaluation
   Finally, we request clarity regarding the anticipated duration of the on-going evaluation. At present, SCID NBS is being delivered without any additional funding or resource support, which continues to place unsustainable pressure on existing services.

Andrew Gennery_SCID_comment from clinician

Name: Andrew Gennery
Email: XXXX XXXX
Organisation: XXXX XXXX
Role: Paediatric Immunologist
Publish submitter's name: True
Publish Organisation name: False

Condition: SCID

My main concern is the inequity of the decision – if your postcode is outwith the 6 English screening areas, you will not be screened and infants will suffer and may die. Additionally, Wales and Scotland are waiting for the English decision before implementing SCID screening (although they could just decide to go ahead) – so infants in these countries are also disadvantaged compared to the English screening regions.

Also, the committee are concerned that the false positives lead to 'untreatable' conditions being picked up. Actually, none of the conditions currently being screened

can be cured – only ameliorated by drugs or diet manipulation. SCID can be cured, as can some of the other conditions picked up as false positives e.g. DOCK8 deficiency. However, picking up the other conditions, in many cases, will allow interventions which will improve the life journey of patients/families – e.g. a diagnosis of DiGeorge syndrome will enable access to speech therapy, educational support (I recently saw an XXXX XXXX year old who had only been diagnosed this year).

Ben Shillitoe_SCID_Comment from clinician

Name: Ben Shillitoe
Email: XXXX XXXX
Organisation: Sheffield Children's Hospital
Role: Consultant in Paediatric Immunology and Infectious Diseases
Publish submitter's name: True
Publish Organisation name: True

Condition: SCID

The SCID Newborn Screening (NBS) programme demonstrates clear clinical benefit, and it is encouraging that this evaluation confirms the findings of previous work. In line with the current report, we have a number of comments and questions that we feel should be addressed before consideration of wider implementation.
From a clinical perspective, we strongly support the need to standardise follow-up and management of incidental idiopathic T-cell lymphopaenic infants identified through this pathway. This "new" cohort generates a significant workload, and it is unclear whether our current practice in follow-up and management is consistent with that of other centres.
The costing model presented appears fair and robust, providing a realistic assessment of current expenditure. However, we have several concerns regarding costs and logistics, particularly in relation to non-HSCT centres. Should SCID NBS be introduced nationally, careful planning will be required to ensure equitable logistics and sustainable funding. Our centre, for example, serves a large geographical region as the sole commissioned Paediatric Immunology centre for South Yorkshire, Humber, Lincolnshire and Derbyshire, with some patients travelling up to six hours to attend and return home. It remains uncertain whether all "suspected SCID" infants would be expected to travel to their nearest specialist centre, or whether local

hospitals would be supported to participate more directly.

A UK-wide SCID NBS programme would require additional support for local centres, particularly in the management of premature infants. This issue is likely to become more prominent if more Level 1/2 centres from district general hospitals are included.

While the programme is not currently considered cost-effective, it is important to note that potential cost savings primarily benefit HSCT centres rather than referring immunology services. The principal financial savings of SCID NBS relate to preventing infectious complications; however, severely affected infants are generally transferred early to HSCT centres, and thus the greatest cost burden of symptomatic SCID patients is borne by these services.

The ongoing evaluation continues to place considerable pressure on clinical, nursing, and administrative staff. We therefore believe that, if SCID NBS were to be rolled out nationally, additional funding and resource allocation would be essential to ensure the sustainability of services managing these cases.

We also wish to highlight that the evaluation does not currently account for SCID-suspected infants who die before confirmatory flow cytometry, and recommend that future assessments include this group.

Finally, we seek clarification on the anticipated duration of the evaluation. At present, no additional funding or resource is provided for SCID NBS, which continues to place strain on our service.

Name: Jeremy D Penn
Email: XXXX XXXX
Organisation:
Role: Volunteer, advocate, and parent
Publish submitter's name: True
Publish Organisation name: False

Condition: SCID

The decision whether to offer newborn screening for SCID as population screening for babies in the UK appears to hinge on an analysis of the cost effectiveness of SCID newborn screening. The cost effectiveness study found a cost of £80,000 to £90,000 per QALY, which the evaluation report notes is "above the threshold usually considered cost effective" (p. 6). After a careful reading of the cost effectiveness evaluation, I have several concerns I would like to bring to the attention of the committee:

- Cost effectiveness studies are notoriously difficult to complete with full accuracy and fidelity, particularly in newborn screening for rare diseases. As pointed out by Prosser, Grosse, Kemper et al. (2012), “data limitations are particularly salient for newborn screening candidate disorders due to the low incidence and the long time frame over which outcomes need to be considered” (https://www.nature.com/articles/gim201224). The low incidence of SCID produces tremendous difficulty in determining reliable estimates for many of the quantities used in the cost effectiveness study, suggesting the use of caution when interpreting the findings from the cost effectiveness study. Further, the heterogeneity of SCID – in its incidence, presentation, severity, and treatment needs – indicates the cost effectiveness could vary widely from year-to-year. As seen clearly in this cost effectiveness report (compared to the prior one completed in 2017), small changes to initial estimates can result in vastly different cost effectiveness findings. This is an artifact of the study process and the nature of rare diseases and should be considered with great caution rather than as a definitive finding.
- The cost effectiveness model appears to significantly over-estimate the long-term survival of symptomatic (non-screened) SCID babies. Figure 8 (p. 23) models the 10-year survival of the symptomatic (non-screened) SCID babies as 70%, or 0.70. Yet, during the evaluation period 5 out of 7 symptomatic (non-screened) babies died, for a survival rate of only 29% (0.29). Similarly, a 2011 study on symptomatic (non-screened) babies in the UK found a survival rate of only 40% (https://www.sciencedirect.com/science/article/pii/S0006497120412182, Brown et al.) compared with a survival rate of 90% for the siblings who could progress to treatment prior to experiencing dangerous infections.
- The cost effectiveness model also misinterpreted research findings that resulted in an over-estimate of the long-term survival of symptomatic (non-screened) SCID babies. For instance, the cost effectiveness study cites Thakar, Logan, Puck, Dunn, Buckley, Cowan, et al. (2023, citation #21) for use in estimating the long-term survival rate of symptomatic (non-screened) babies with SCID. On page 25 of the cost-effectiveness report, the cost effectiveness study claims Thakar et al. (2023) had a 5-year survival rate of symptomatic (non-screened) SCID babies of 79.9%. However, a careful reading of the Thakar et al. (2023) study reveals it included ONLY patients who “underwent HCT between Jan 1, 1982, and Dec 31, 2018” (p. 130). Thakar et al. did NOT include symptomatic (non-screened) SCID babies who died prior to progressing to HSCT in its survival estimates. Therefore, the true survival rate of symptomatic (non-screened) SCID babies in the Thakar et al. (2023) study was much lower; the 79.9% rate should NEVER have been used to inform the survival rate estimate in the cost effectiveness study

because the cost effectiveness study is seeking a survival rate for ALL SCID babies, not just those who survive long enough to progress to HSCT.

- Similarly, the Hardin et al. (2022) study is used in multiple places throughout the cost effectiveness study to provide estimates of long-term mortality rates for individuals with SCID (for example, see p. 25). However, the Hardin et al. (2022) study used essentially the SAME data set as the Thakar et al. (2023) study (although with a slightly extended cutoff date to August 1, 2019, slight variation in inclusion criteria, and supplemented with a survey of patients). These data include ONLY patients who survived long enough and were healthy enough to receive a bone marrow transplant (HCST). This leaves out the large number of SCID babies who became ill with a serious infection and died prior to being eligible to receive a HCST. Therefore, just like the Thakar et al. (2023) study, the Hardin et al. (2022) estimates should NOT be used as estimates of long-term survival for symptomatic (non-screened) SCID babies. The actual survival rate of symptomatic (non-screened) SCID babies is much lower; in fact, Hardin et al. (2022) point out, “this condition is universally fatal in the first or second year of life unless definitively treated” (p. 1077).
- The retrospective SCID Cohort data from GOSH and NUTH presented in Table 19, and used to support an estimate of long-term survival of symptomatic (non-screened) SCID babies of 70%, also likely experiences a similar bias in that, in the absence of screening, those with the most severe types of SCID – and thus the most likely to benefit from screening – are the most likely to die prior to having their SCID diagnosed and are therefore left out of the retrospective analysis. In addition, SCID babies that live away from the GOSH / NUTH service areas that become sick may be unable to travel to receive treatment at those facilities, resulting in their death prior to their diagnosis with SCID and without their inclusion in the retrospective cohort.
- Another source of bias in the GOSH / NUTH retrospective data is that these two centers are globally recognized centers for treating SCID and therefore attract patients in a non-random manner who are demographically different from the overall population. Specifically, families with a history of SCID may seek out care at NUTH / GOSH for future children, which would inflate the proportion of family history cases (reported as 25%, which is high given that prior research has suggested family history identifies fewer than 20% of all cases (see: https://pmc.ncbi.nlm.nih.gov/articles/PMC4433840/)). NUTH / GOSH, as globally recognized centers for SCID care, tend to attract families who are wealthier and more able to travel to receive medical care than in the broader population. This produces a bias in the survival estimates because it is not a true sample from the broader population but rather represents a specific subset of SCID patients. Importantly, survival for patients treated at hospitals, particularly specialized hospital centers, will ALWAYS be higher

than survival in the population. As a result, the GOSH / NUTH retrospective data overestimate the survival of SCID babies in the population and should be revised downward or not used at all in the estimation of likely population survival rates.

- Therefore, the estimated survival rate of 70% (0.70) in the cost effectiveness study appears to significantly over-estimate the long-term survival of those SCID babies not identified through screening or family history. Using a much lower, more accurate, survival rate in the model would have the effect of increasing the QALYs produced from newborn screening for SCID and thereby significantly improving the cost effectiveness of SCID newborn screening.
- The cost effectiveness study also appears to misinterpret the findings from the Lankester et al. (2022) study. The cost effectiveness study claims the Lankester et al. study found “no significant difference” between SCID patients transplanted at <3.5 months and those transplanted later (p. 25). While technically accurate, this does not tell the full story. A careful reading of the Lankester et al. study shows the researchers found a “strong negative impact” of pretransplantation infections, causing significantly worse survival rates in those who experienced infections (73%) compared to those who did not (87%) (p. 1747). While it is true an increased age at transplantation was not associated with worse outcomes in that study, delays in getting to transplantation puts babies at a higher risk of infection which significantly lowers survival. The Lankester et al. (2022) study should therefore not be considered as evidence against early transplantation, as it clearly shows benefits in getting infants with SCID to transplantation as quickly as possible, as delays increase the chance that SCID babies will receive serious infections and will die prior to reaching transplantation. This finding – that infection due to delays in progressing to HSCT – is supported by many other studies (see: https://link.springer.com/article/10.1007/s12016-024-08993-5).
- The cost effectiveness study appears to under-estimate the cost of providing care for symptomatic (non-screened) SCID babies prior to their diagnosis and HSCT. The reported cost of £79,531 in the first two years for symptomatic (non-screened) SCID babies includes only admitted patient care, outpatient care, and emergency department activity. Notably, it does NOT include important family costs, such as parents’ missed work due to the baby’s illness, transportation to and from additional medical visits, out-of-pocket purchase of medicines or other care items (such as humidifiers, blankets, and other illness care products), care provided by other family members, or other important non-financial costs to families such as increased family stress and decreased time available to engage in leisure or recreation or provide care for other children or adults in the family. A meta-analysis on costs and cost

effectiveness for immunodeficiencies (Elsink, van Montrans, van Gijn, et al., 2020) found “early diagnosis leads to overall cost savings” (p. 6) when a broader range of costs were analyzed.

Due to these errors and the many unaccounted sources of bias in the cost effectiveness study, I have little confidence in the conclusion that the “cost effectiveness of screening for SCID has gone from £18,222 per QALY gained in the original analysis to £87,813 here” (p. 65). I am deeply concerned that this error-prone and biased result, which significantly inflated the true cost effectiveness of newborn screening for SCID, will result in the UK’s rejection of population newborn screening for SCID.

Given the significant issues with the cost effectiveness study, I see two possible pathways forward.

The first option is to continue and expand the current pilot program for SCID newborn screening. This would allow the UK to collect additional information about long-term outcomes and better, more in-depth information about other costs, such as additional family-related costs (such as time away from work to care for a sick baby), that were ignored in the present model. The collection of additional data may allow for somewhat higher levels of confidence in future cost effectiveness analyses.

The second option is to move forward with population screening for SCID. There are strong data that newborn screening for SCID produces health benefits for babies, shortens the time to diagnosis, improves the outcomes of HSCT, and is acceptable by parents. This pathway may bring some uncertainty around cost effectiveness. Unfortunately, it seems possible that a fully accurate and complete cost effectiveness study may be impossible to complete, even with additional years’ data, given the constraints of a rare condition and ethical considerations around failing to provide access to treatment for babies identified through epidemiological studies. Rather than focusing attention on the deficiencies of cost effectiveness studies, I encourage committee members to consider a different question instead: is the cost of newborn screening for SCID reasonable, given its benefits? Instead of asking academic questions about how to best calculate QALYs and estimate the financial ripple effects of a change in a very complex medical system, try simply asking parents if they would be willing to spend £7.53 to protect their baby, and their neighbors’ babies, from avoidable complications and possible death from SCID. Viewed in this light, the costs of screening for SCID appear very reasonable, indeed.

I encourage the committee to select one of these two pathways. A third choice, one that I hope the committee will not consider with any seriousness, is to end newborn screening for SCID altogether and rely on symptomatic or family identification of SCID cases going forward. This option would be a disaster for all the families affected by immune deficiencies. It would increase health inequities by putting up

additional barriers to low-income families and those located farthest away from NUTH / GOSH in seeking care for their children. It would be unethical, by limiting access to known successful treatments for those who need it. And, most importantly, it would undermine NHS's mission to provide high quality healthcare to all.

Thank you for the opportunity to provide feedback into this important decision. Please let me know if I can provide additional comment or input.

Sincerely,

Jeremy D. Penn, Ph.D., M.P.H.

Iowa, United States

Educator, advocate, SCID parent

Name: Paul Torpiano
Email: XXXX XXXX
Organisation: British Paediatric Allergy, Immunity and Infection Group
Role: National representative for immunology
Publish submitter's name: True
Publish Organisation name: True

Condition: SCID

As the British Paediatric Allergy, Immunity and Infection Group, we:

1. Disagree with suspending the newborn screening (NBS) for Severe Combined Immune Deficiency (SCID) programme in view of lack of evidence to support cost-effectiveness in the UK.
2. Agree with the suggestion to combine SCID and SMA screening in an attempt to make the programme more cost-effective.
3. Are concerned that extending the current pilot screening for NBS SCID screening will:
   a. Lead to an interim service that is unstructured and underfunded.
   b. Lead to inequity in childcare across the UK, with children born in certain postcodes benefiting from NBS SCID Screening, while those born outside of such postcodes only diagnosed upon presentation with infection, with expected impact on their course and outcomes.
4. Support the recommendation to implement reflex genomics to reduce the number of false positive results from the NBS SCID screening programme.

5. Support the recommendation for incorporating the results of the BCG programme into reviews and planning around the NBS SCID programme.
6. Support the recommendation for the implementation of clinical protocols for the management of non-SCID T-cell lymphopenia to ensure consistency in management.

Rationale:

1. SCID is a life-threatening diagnosis, and it is our experience that diagnosis soon after birth (i.e. before exposure to infection occurs) allows timely intervention with bone marrow transplant, gene therapy or thymic transplant with superior clinical outcomes compared with when the same interventions are performed in children who present with poor health and/or a significant infection burden.
2. Since the ongoing pilot NBS SCID programme is limited to the 6 English screening areas, maintaining the restricted programme as it is for the foreseeable future risks generating inequity, as children born outside of these areas will not have access to this essential aspect of neonatal and paediatric care.
3. The suggestion to reduce the costs of the NBS SCID programme by combining it with a purported Spinal Muscular Atrophy screening is reasonable and welcome. However, we express concerns that until such a programme is established, the NBS SCID programme risks being unstructured and underfunded in a way that makes it difficult to maintain as an effective service.
4. Finally, we would argue that many countries across the world have already implemented similar NBS SCID programmes, with excellent results. Without the adoption of such a programme in the UK, children born here will be disadvantaged from very early on from a healthcare perspective compared with those born overseas.
5. Cost-effectiveness is of course a key aspect to any national screening programme, however:
   a. There is already data to support cost-effectiveness of such a screening programme from outside of the UK, and though local data is needed to support local implementation it is difficult to dismiss newborn SCID screening as financially unsustainable in the light of such international data.
   b. Accurate quantification of the financial benefits of a NBS SCID programme may be difficult to obtain and liable to underestimation. Early identification of SCID prevents complications with infection which may be varied in

microbiological cause, clinical presentation and course, and response to treatment. Managing such an infection burden is inevitably costly, and the more complicated the infection, the higher the costs – and largely unpredictable.
Furthermore, the NBS SCID programme has been shown to improve mortality with SCID, and it is equally very difficult to quantify the financial burden of a preventable child death, which may have implications for parental and sibling wellbeing and mental health, family financial status and parental work performance, and recourse to support structures that might otherwise be unnecessary.

Name: XXXX XXXX
Email: XXXX XXXX
Organisation: Manchester University NHS Foundation Trust
Role: XXXX XXXX
Publish submitter's name: True
Publish Organisation name: False

Condition: SCID

Manchester Newborn Screening Laboratory Response:
Manchester Newborn Screening Laboratory fully supports the proposal to extend the SCID in-service evaluation. As users of the Revvity EonisQ method, introduced in November 2023, it would be useful to gain further experience with the performance of this method across different lot numbers and with optimised cut-offs. Our current workflow could very easily be adapted to include SMA screening, as this test is available on the same kit as for SCID. In terms of training competencies, equipment maintenance and IT configuration, it would be detrimental to stop SCID screening then resume later or switch to SMA screening alone, at a later date. Regarding exploring 2nd line genetic testing for SCID, in Manchester, we're in a particularly good position to work closely with our genomic colleagues as we are co-located with the North West Genomic Laboratory hub in St. Mary's Hospital. A major challenge in taking part in this ISE has been recruitment and retention of skilled staff on short-term contracts. This needs to be considered in the extension of this ISE and in the design of future ISEs.

Name: XXXX XXXX
Email: XXXX XXXX
Organisation: XXXX XXXX
Role: XXXX XXXX NBS Laboratory XXXX XXXX
Publish submitter's name: False
Publish Organisation name: False

Condition: SCID

> Kansas has been screening SCID for approximately 8 years. We have a lower cutoff and a high false positive rate. We are getting babies diagnosed for SCID, DiGeorge, T-cell lymphocyte deficiencies, B-cell lymphocyte deficiencies, NK-cell lymphocyte deficiencies, hematological disorders and leukemia. That is not really our goal, as screening SCID is our goal, but our program is proud of being able to help those babies who might not have been diagnosed with those disorders. We can raise our cutoff to catch SCID only, which would be a recommended 40 Ct through RT-PCR. We do not perform any sequencing on SCID as those variant numbers are excessive. We do recommend flow cytometry with CBC for those who screen out of range. I am not a clinician but would recommend a higher cutoff to at least catch those babies who may have the immunodeficiency disorder than to not screen any babies for SCID at all.
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Name: Paul Torpiano
Email: XXXX XXXX
Organisation: Immunology Consultant Team, Immunology Department, Directorate for Blood, Cells and Cancer, Great Ormond Street Hospital for Children NHS Foundation Trust
Role: Consultant in Paediatric Immunology
Publish submitter's name: True
Publish Organisation name: True

Condition: SCID

Main points:
As the GOSH Immunology consultant team, we:

1. Disagree with suspending the NBS SCID programme in view of lack of evidence to support cost-effectiveness in the UK and fully support a continued screening programme.

2. Agree with the suggestion to combine SCID and SMA screening in an attempt to make the programme more cost-effective.

3. Are concerned that extending the current pilot screening for NBS SCID screening will:
   a. Lead to an interim service that is unstructured and underfunded – and therefore unsustainable in its current format.
   b. Lead to inequity in care across the UK, with children born in certain postcodes benefiting from NBS SCID Screening, while those born outside of such postcodes will only be diagnosed upon presentation with infection, with expected impact on their course and outcomes.

4. Support the recommendation to implement reflex genomics to reduce the number of false positive results from the NBS SCID screening programme.

5. Support the recommendation for incorporating the results of the BCG programme into reviews and planning around the NBS SCID programme.

6. Support the recommendation for the implementation of clinical protocols for the management of non-SCID T-cell lymphopenia to ensure consistency in management.

Rationale:

1. SCID is a life-threatening diagnosis and it is our experience that diagnosis at birth (i.e. before exposure to infection occurs) allows timely intervention with bone marrow transplant, gene therapy or thymic transplant with superior clinical outcomes compared with when the same interventions are performed in children who present with a significant infection burden.

2. Cost-effectiveness is of course a key aspect to any national screening programme, however:
   a. There is already data to support cost-effectiveness of such a screening programme from outside of the UK, and though local data is needed to support local implementation it is difficult to dismiss newborn SCID screening as financially unsustainable in the light of such data.
   b. We would argue that an accurate quantification of the financial benefits of a NBS SCID programme may be difficult to obtain and liable to underestimation. Early identification of SCID prevents complications with infection which may be varied in microbiological cause, clinical presentation and course, and response to treatment. Managing such an infection burden is inevitably costly, and the more complicated the infection, the higher the costs – and largely unpredictable.
   Furthermore, the NBS SCID programme has been shown to improve mortality with SCID, and it is equally very difficult to quantify the financial burden of a single preventable child death, which may have implications for

parental and sibling wellbeing and mental health, family financial status and parental work performance, and recourse to support structures that might otherwise be unnecessary.

3. The suggestion to reduce the costs of the NBS SCID programme by combining it with a purported Spinal Muscular Atrophy screening is reasonable and welcome. However, we express concerns that until such a programme is established, the NBS SCID programme risks being unstructured and underfunded in a way that makes it difficult to maintain as an effective service.
4. We also express concerns that since the ongoing pilot NBS SCID programme is limited to the 6 English screening areas, maintaining the restricted programme as it is for the foreseeable future risks generating inequity, as children born outside of these areas will not have access to this essential aspect of neonatal and paediatric care.
5. Finally, we would argue that many countries across the world. Independent of gross domestic product, have already implemented similar NBS SCID programmes, with excellent results. Without the adoption of such a programme in the UK, children born here will arguably be disadvantaged from a healthcare perspective from very early on compared with those born overseas.

Name: Sue Dimmock
Email: XXXX XXXX
Organisation: UK Primary Immune-deficiency Patient Support
Role: Joint-Chair
Publish submitter's name: True
Publish Organisation name: True

Condition: SCID

UKPIPS is a small volunteer-led charity supporting anyone with an inborn error of immunity and specifically primary immune and antibody deficiencies. UKPIPS fully supports the recommendation to continue the in-service evaluation (ISE) of newborn screening for severe combined immunodeficiencies (SCID) in NHS services.

It is vital that all parents with children potentially impacted by SCID have the reassurance they need to know that the condition will be identified; referred and

managed by professional specialists in immunology at the very earliest opportunity. Children affected by SCID need all of this in place to give them the best possible outcomes in life. The NHS needs this in place to reduce the unnecessary cost of children being hospitalised with significant, life-threatening infections or other life-threatening complications that may go (and historically have gone) undiagnosed for too long.

Name: Monica Thakar, MD

Email: XXXX XXXX

Organisation: Pediatric Immune Deficiency Treatment Consortium

Role:

Publish submitter's name: True

Publish Organisation name: True

Condition: SCID

We appreciate the opportunity to provide comments to the UK NSC regarding the decision to not include SCID on the UK newborn screening panel at this time. Our research group, the Pediatric Immune Deficiency Treatment Consortium (PIDTC), consists of stem cell transplantation and immunology physicians in the United States and Canada. We work in collaboration with clinicians, scientists, and families to study SCID and other primary immune deficiencies, from diagnosis through curative therapies. Through our collection of natural history studies, and now prospective treatment studies, we have provided detailed analyses resulting in 79 publications since 2008, which now represent 45 active centers in the US and Canada. Our group is heavily invested and knowledgeable in diagnosing and treating this set of disease. We read with interest that one of our articles was cited in the SCHARR cost-effectiveness analysis [page 25, paragraph 2; citation #21]. In the SCHARR report, the benchmark 5 year survival for those patients diagnosed by clinical presentation was 79.9%. We believe that this number (79.9%) was inaccurately used to represent the estimated rate of survival for SCID. This is incorrect as it represents only those children who survived to be able to undergo hematopoietic cell transplantation (HCT), and does not include those patients who died prior to HCT. Using 79.9% in the

modeling would result in a lower quality-adjusted life year (QALY) estimate and an over-estimated cost per QALY saved. Our study does not provide any information on SCID survival in the absence of NBS. We understand that many factors are evaluated when determining disease fitness for inclusion in a national screening program. If these QALY data estimates were a significant reason to decline SCID NBS in the UK, we respectfully ask the committee to review their recommendations as the models seem to begin with data that is not accurately represented.

Respectfully submitted by Monica Thakar, MD, on behalf of the PIDTC

Name: XXXX XXXX Email address: XXXX XXXX

Organisation (if appropriate): Immunodeficiency UK

Role: CEO

Do you consent to your name being published on the UK NSC website alongside your response? Yes No *(delete as appropriate)*

You are invited to provide feedback on any or all of the following documents: the UK NSC cover note and recommendation, the UK NSC evidence summary, the NHS England ISE report and the SCHARR modelling study

Document, section and/or page number	Text or issue to which comment relates	Comment *Please use a new row for each comment and add extra rows as required.*
N/A	SCID NBS ISE	Immunodeficiency UK would like to thank the project board, SCHARR team, the laboratory staff, and the immunology teams involved in the SCID NBS ISE. You have faced many challenges, and your stamina and dedication in finding solutions to make the pilot work have been amazing. Your work has helped save the lives of many babies affected by SCID. If you need evidence of this, please read XXXX XXXX story My family and SCID by Jennifer - Immunodeficiency UK,
NHSE	Changes in BCG vaccination programme. Page 14.	One of the remarkable feats of the pilot was the cross-working of agencies to change the timing of BCG vaccinations to ensure babies with a screen-positive SCID result did not

In-Service Evaluation of SCID report		develop BCGosis, a condition which can result in poorer outcomes for those affected. As shown by the data obtained during the pilot, the evidence is that SCID screening will reduce the number of BCGosis cases. In contrast, the resulting health complications and mortality due to BCGosis of SCID babies who were not in the pilot screening areas were a stark and sobering reminder of why the change was needed. It is also reassuring to know that there is now a much-improved system of collecting BCG vaccination uptake data!
NHSE	Page 5 and other mentions of countries where SCID screening is implemented nationally.	The report should have listed in full the countries where there is a national programme of SCID NBS screening. This would set the UK situation in context. According to the PID Life Index data run by IPOPI Ipopi - PID Life Index the following countries have already fully implemented national SCID screening: Spain, Iceland, Norway, Sweden, Finland, Ukraine, The Netherlands, Germany, Denmark, Austria, Slovenia, France, Portugal, Ireland, Israel, Australia, New Zealand, USA and Canada. This list indicates rather more than 'some other countries'.
In-Service Evaluation of SCID report	Quote: 'Newborn screening for SCID is already offered in most of the USA and some other countries.'	The news that the recommendation is not to roll out a national screening programme for SCID in the UK is devastating. Although the rationale for this decision is clearly costed, it is nonetheless shocking that the UK lags so far behind other countries in implementing SCID national screening. This raises the question about the differences in how screening programmes in other countries are assessed compared to the UK, and indeed whether the UK places a lower value on the cost of saving a baby's life.

SCHARR report	Parental HRQoL impacts resulting from bereavement	It is unclear that this impact adequately reflects the situation in SCID screening, where the clear intention is to prevent death through early intervention. It seems probable that the course and impact of bereavement must be different for parents who have lost a child to SCID because they lived in an area not covered by the pilot. Knowing that if you lived in a screening area could have saved your child's life through earlier intervention must be truly devastating for parents.
SCHARR report and NHSE report	Section 3.7.1	Were the impacts on these families researched in the same in-depth way as the false positives? If not, they should be. There is bias and emphasis on false positives, and no mention of the positive impact of a true SCID positive result, which can result in the saving of a dearly loved child for its parents and extended family.
SCHARR report and NHSE report	QUALY threshold as a benchmark for acceptance for a national screening programme.	The QUALY threshold of £30k has remained unchanged since 2004. Over the last 20 years, the cost of treatment and care has risen substantially, with vast improvements in the range of treatments available for SCID, including HSCT, gene therapy and thymic transplant. The QUALY threshold has not kept pace with advances and inherently means this threshold is an unfair barrier. NICE and the NHS have already accepted a higher cost threshold for the above-valued treatments for SCID; yet, the cost of the SCID NBS programme, which would save more children's lives through these treatments, is currently considered prohibitive. This is a conundrum.
SCHARR report	Page 5 Impact of falling birth rate on cost effectiveness.	Is a falling birth rate and consequences on cost effectiveness a justifiable reason for not implementing a SCID NBS screening programme? Will the current programme of NBS conditions be re-evaluated in light of falling birth rates?
NHSE report	Page 9	Flaws in the consent process of screening e.g. lack of recall by false positive families)

		should not be used as a reason to hinder the rollout of SCID NBS.
UK NSC report	Supporting the continuation of the SCID ISE	Short of a full national rollout, Immunodeficiency UK supports the recommendation to continue the SCID ISE in tandem with screening for SMA. This would, however, continue the inequity for SCID across the UK, which will lead to the deaths and poorer outcomes of babies with SCID in non-screened areas, who present later with symptoms. This is evidenced by the stark contrast of the survival data from screened and non-screened areas of England (92% survival versus 29%).
		We support the use of 'reflex genomics' to reduce the number of false positives. Furthermore, it would make sense to include SCID genes and a broader range of actionable conditions, considered relevant to TREC screening, using the Generation Study list of conditions as a model. Experts in these conditions should be consulted for an informed, agreed approach.
	Ditto	Clarity is needed regarding how long the joint SMA/SCID ISE would last and on the structure of the oversight group. The screening for SCID project has been on-going since 2017. How much longer does the UK have to wait for full implementation of national SCID screening?
		The knowledge gaps mentioned in the reports must be filled in any future phase of the SCID NBS and must be supported by funding.
	Ditto	It is noted that the following are needed: 1. 5-year follow-up of SCID babies detected by NBS. 2. Non-SCID -T-cell lymphopenia prognosis study and development of care pathways and clinical management guidelines. This is

		deemed fundamental to establish criterion 4 (Rapid evidence review).
		The mental strain and anxiety caused by the impact of the SCID diagnostic odyssey for families in areas where screening is unavailable should be evaluated. There must be plans in place to ensure that both lab services and immunology services involved in an SCID NBS programme have the necessary infrastructure and workforce. At present, the Royal College of Pathologists indicates that clinical immunology services are in a fragile state Briefing-RCPath-Clinical-immunology-workforce-2025.pdf.
	Ditto	
NHSE report	Page 48: Incidental findings and additive value of SCID screening.	There is little point to the UK's ambition of screening for more conditions through NBS or genomics programmes if there is inadequate infrastructure and manpower within the NHS to deliver the screening programmes, and subsequent care for the affected families. In addition to the 10 SCID babies, who were detected by screening, it is satisfying to note that there were benefits to more children's lives through the pilot. These included babies with Di George syndrome, FOXN1, STAT2, ligase 4 deficiency and cartilage hair hypoplasia. These are conditions that would not otherwise have been recognised so early, and this means meaningful health interventions can be made.
NHSE full report	Page 63	In the absence of the rollout of a full UK-wide SCID screening programme, Immunodeficiency UK's supports the recommendations on page 63.
		Immunodeficiency UK agrees that there needs to be financial support available for families to travel to access confirmatory

testing. Psychosocial support is also essential.

Name: Patricia Roberts
Email: XXXX XXXX
Organisation: ArchAngel MLD Trust
Role: Director for Newborn Screening
Publish submitter's name: True
Publish Organisation name: True

Condition: SCID

I leave the technical observations to scientific, clinical and SCID patient organisation colleagues. These are therefore our general comments:

1. We believe that it will give unwarranted suffering to children by delaying the implementation of NBS for SCID and introducing a further extended period of the ISE. The ISE 2021-24 has identified some issues that can be resolved through live programme running, however it has demonstrated that SCID screening will do more good than harm at reasonable cost. (Exec Summary and p5). There is clear evidence on survival benefits for screened babies. It is unethical to delay this any longer.
    1. Extending the ISE prolongs inequitable access to screening and treatment which goes against the health inequalities framework.

    2. Criteria 4. Acceptability of screening by parents and carers.
    Usually the UK NSC observes they do not have opinions of, or data on, those parents with healthy babies or indeed the general population. In the case of SCID they accept that they do have evidence from involved parents and carers and that screening is acceptable to them. Parents believe that screening for SCID conditions was beneficial regardless of treatability.
    However they do not have the information set from parents and carers involved in SCID screening where the child has received a false or different result. We find it difficult to understand why this is only just being raised as an issue in the 2025 Evidence Review and was not included in the scope of the ISE between 2021 and 2024. Why was one included and not the other? Why was it not identified and included during the 3 year period? It surely cannot now use it as an argument to reject screening or extend the ISE. It is almost like changing the normal UK NSC argument around to justify and prevent implementation of SCID!

    3. SCID was first proposed as a candidate for NBS in the UK in 2011. We are now 14 years on. This is just unacceptable. Over 20 Countries now screen for SCID. This has now gone beyond establishing that screening for SCID is appropriate for the UK population and can be assimilated into the laboratory and other processes. Why is an extension of the ISE even being considered. Nothing in the Evidence Review can

justify this. Surely outstanding issues can be resolved in live screening. This has happened in other disorders that have been implemented. How many more babies have got to die or live with life limiting conditions.

4. The cost effectiveness study demonstrates that SCID screening is cost effective when combined with SMA screening. Both should be implemented without unecessary delay to prevent further loss of life or life limiting disability.

Name: Rosanna Flury (on behalf of the BSI-CIPN)
Email: XXXX XXXX
Organisation: British Society for Immunology Clinical Immunology Professional Network
Role: Programme Manager – Clinical
Publish submitter's name: True
Publish Organisation name: TrueCondition: SCID

British Society of Immunology Clinical Immunology Professional Network (BSI-CIPN) response to the public consultation on the in-service evaluation of newborn screening for Severe Combined Immunodeficiency Disorder.Summary of Recommendations

· Although not cost effective, the SCID newborn screening programme has been found to be extremely clinically effective. The full economic cost-effectiveness of the programme is likely to have been underestimated (see below), and with adaptations to the screening protocol could be improved. Terminating the newborn screening programme for SCID would be a significant retrograde step in clinical management and a severe blow to the immunodeficiency community.·

If combined with SMA newborn screening then it is likely that screening for both diseases will become cost-effective, and we would recommend continuing the SCID newborn screening programme until evaluation of SMA screening is complete.

· We recommend extending screening to the whole of the UK, as the current geographical inequity of care is an ethical and prejudicial.·

We welcome a review of the genetic testing support for the SCID newborn screening programme. We have concerns about referring patients directly for genetic testing without flow cytometry testing as this will increase the risk of missing significant immunodeficiency diagnoses which could result in avoidable death or morbidity. Any adoption of reflex genetic testing should be carefully risk assessed and should be subject to careful ongoing audit.·

We support the long term follow up of true positive patients from the newborn screening in-service evaluation as this will give invaluable clinical and health economic outcome data on the true benefits of screening.·

We agree with the need for additional work on parent information and newborn screening counselling to reduce the impact of false positive screening tests.·

We agree with combining monitoring of the BCG vaccination programme with the SCID newborn screening programme as these are inexorably linked.·

We support the standardisation of expert consensus clinical algorithms for the management of non-SCID T-cell lymphopenia, and would support the long-term follow-up of this important cohort of patients.

Clinical effectiveness

The in-service evaluation clearly demonstrates a marked clinical effectiveness of SCID newborn screening with 92% survival for SCID babies diagnosed through the newborn screening programme compared to 20% in the clinical presentation cohort. Many patients incidentally diagnosed with non SCID T-cell lymphopenia had already gained benefit from newborn diagnosis. The full clinical and economic benefits for this cohort of patients will only be fully appreciated in decades time. We know that patients who present clinically with non-SCID T-cell lymphopenia disorders usually already have established end-organ damage and lifelong significant health needs. Early diagnosis offers an opportunity to improve clinical outcome in these patients and reduce their high health economic burden.SCID newborn screening was welcomed by all parents. Despite the problems with the test's low positive predictive, high numbers of false positives and the distressed caused by false positive results, parents and healthcare professionals have all been highly supportive of the screening program. Observations on epidemiology during in-service evaluationData generated during the in-service evaluation of SCID newborn screening pilot, illustrates the complexity and pitfalls of population studies in rare diseases. Despite an evaluation period of 2.5 years the birth prevalence of SCID during this period was 1 in 71000, despite a historical UK prevalence of 1 in 53000, and a prevalence of 1 in 33000 in the 12 months following the pilot study. Most European countries and the US where newborn screening has been implemented, have reported a SCID prevalence of between 1 in 50000 and 1 in 60000. Furthermore, 30% of the SCID babies diagnosed through newborn screening had a recently identified genetic defect (first published during in-service evaluation) or remained genetically undefined. This is far higher than that seen in published cohorts where approximately 85% of SCID babies having "typical" SCID genetic defects. The definitive treatment outcomes (and therefore healthcare costs) associated with these novel disorders are likely to be more unpredictable and higher. The results from the in-service evaluation illustrate the vast random variability of rare disease year on year prevalence. This introduces potential inaccuracies in extrapolating this data to longer term service evaluation. The cost effectiveness evaluation highlighted that the cost effectiveness of SCID screening markedly improved at higher disease prevalence, and this combined with the atypical diagnoses made by the screening programme is likely to have negatively impacted on the cost effectiveness of the screening programme.Quality of life analysis and full economic cost of screeningThe economic analysis of newborn screening for SCID has still only been assessed over a relatively short period of time. As clinicians looking after generations of families who have lost 1 or more baby with SCID, we would suggest the full economic impact of a SCID baby's death is underestimated in this analysis. Because of the highly traumatic and psychologically

disturbed journey a family has to endure following a clinical diagnosis of SCID (> 6 months inpatient hospital stay, large distances from the family home, prolonged stays on PICU, communication barriers due to language issues, prolonged and distressing deaths), it is very common to see families affected by long term mental health problems, self harming, suicide and attachment/relationship issues with other siblings. This represents a large but hidden economic burden of these diseases.Within the cost effectiveness report, the QALY dis-benefit of parents receiving false positive results outweighs the QALY benefit of the bereavements avoided through newborn screening. The report also highlights that almost all parents were not aware that SCID was being screened for. Improvements in the perinatal newborn screening counselling and the information provided for parents would reduce the QALY dis-benefit of false-positive results, and re balance the QALY benefit analysis.Full economic benefits of SCID newborn screeningThe in-service evaluation performed provided an incomparable and exhaustively detailed comparison of 3 diagnostic platforms and a variety of diagnostic threshold cut offs. This has provided a detailed description of strengths and weaknesses of the screening options available but delivering newborn screening in this setting is more expensive than any real-world diagnostic which would be adopted for a substantive program.Over the long term, cost savings for SCID newborn screening could be achieved by;

· Using tighter positive cut off thresholds or adopting an alternative strategy for premature babies to reduce the number of false positive results.·

Adoption of a single national platform will result in efficiency savings and more efficient trouble shooting for operational problems.·

The cost of SCID newborn screening will reduce over time.·

Given the novel nature of TREC screening (PCR) based, this programme has a higher up-front infrastructure cost associated with it. This infrastructure is likely to be shared with other screening programmes in the future.

Overall, these factors and those discussed in the epidemiology and quality of life comments suggest that SCID screening is likely to be significantly more cost effective than the in-service evaluation suggests in a real world setting over the longer time period.

Genetic testing

Having clear guidelines as to which patients with positive newborn screening tests are referred for genetics would be highly beneficial and would make ongoing evaluation of the newborn screening programme more robust.

Having appropriate funding and support for a rapid genetic test covering a discrete panel of SCID genes would reduce delays in confirming a diagnosis and delivering definitive treatment. The current turn around time of 3 weeks for a whole exome sequence based gene panel, results in delayed treatment and is slower than most other leading European countries. An urgent turn-around test could be combined with genetic investigation for the other immunological emergency, primary

haemophagocytic lymphohistiocytosis. Genetic testing with a 1 week turnaround for these to disorders would significantly improve clinical care and outcome.

Proceeding to reflex genetic testing without flow cytometry for patients with TREC levels on newborn screening which fall below the threshold cut off but are not absent, may reduce the workload of specialist immunology referral centres, but runs the risk of delaying the diagnosis of a serious immunodeficiency, and therefore delaying the instigation of prophylactic treatment. We know there will always be a significant proportion of babies with serious immunodeficiencies who remained genetically undefined, and without performing flow cytometry on these babies they may be lost to follow-up, only presenting critically ill at a later time point.

Inequity of current screening situation

Continuing the SCID newborn screening programme in the current format, would result in a post code lottery of survival for babies born with SCID. This geographical in equity of care is unethical and could potentially lead to a legal challenge by a judicial review.Babies with SCID are disproportionally represented among ethnic minority and families from low socio-economic backgrounds, and therefore termination of the SCID programme would disproportionately disadvantage these patient groups.

International profile

No other country in the world has initiated a national SCID newborn screening program and then terminated the programme. This decision would leave the UK has an outlier in the management of babies with inborn errors of immunity. Reputationally this would significantly damage the reputation of the UK as a leader in the field of inborn errors of immunity and may reduce international investment in research and research collaboration. Such a decision may also be at risk of challenge through a judicial review from individual patients or patient groups.

UK NSC CONSULTATION RESPONSE

27 October 2025

Consultation on whether to extend the in-service evaluation for severe combined immunodeficiency disease (SCID)

Genetic Alliance UK welcomes the opportunity to provide a response to this consultation from the UK National Screening Committee (UK NSC). The NHS England report confirms that the evaluation ran from 2021-2024 and was completed to assess whether screening for SCID would 'do more good than harm at reasonable cost' (NHSE ISE report, p5). The UK NSC has indicated that the ISE may be extended so that SCID screening continues in pilot areas while the SMA ISE proceeds. We have outlined several concerns regarding this position in our response, and elaborated on each below.

It is Genetic Alliance UK's view that the evidence presented does not support extension of the ISE – and thus delay of a recommendation to support screening for SCID is not justified. Screening for SCID is highly cost-effective when implemented alongside SMA, yet the protracted 'decision-pause' at the four-nations level continues to hold back universal access. This is a serious equity concern for our community. Many comparable countries have introduced SCID (and SMA) screening much sooner, meaning newborns in the UK may still be disadvantaged simply by geograph or timing. We therefore urge the UK NSC to recognise the combined SCID and SMA screening as an urgent equity priority, minimise inequitable roll out, and ensure that next steps focus on supporting nation-wide implementation rather than further postponement of a positive recommendation.

1. The ISE found clear benefits for babies with SCID identified through screening. The UK NSC evidence summary concludes that criterion 9, which relates to improved survival through screening, is met for screening-detected SCID (NHSE report p45-47). Further:

- Families whose children were diagnosed without screening faced significantly worse outcomes: Survival was 100% (10 of 10) compared with 20% for those not offered screening.
- Length of hospital stay and use of intensive care were much higher among non-screened infants: Clinically presenting babies faced a PICU stay of 18 days, whereas babies who were identified via screening family history spent zero days in a PICU before treatment.
- Age at definitive treatment was more than double that for families not offered screening (189 days for clinically presenting infants, 79 days for babies detected via screening).

2. Genetic Alliance UK is deeply concerned about the equity implications of extending the ISE for a further four years. The report notes that of the 12 babies found to have SCID, '10 of them, in the absence of screening, would not have presented until symptomatic and would therefore have been more difficult to treat' (p. 11). Since the ISE covered only 6 of the 13 blood spot laboratories, offering screening to around 50% of babies born in England (NHSE p. 21), upholding partial coverage would sustain the existing 'postcode lottery' for access to potentially life-saving screening and treatment. This is in opposition to the PHE screening inequalities framework, which commits programmes to reducing geographic variation and ensuring universal access. Each year of delay compounds the inequity: since ~14 babies annually are expected to be born with SCID, a four-year extension could mean that an estimated 56 newborns may receive different opportunities for a timely diagnosis and potentially curative treatment based on where they are born in England.

3. The ISE findings show that national roll out of SCID screening is not only reasonable cost, but operationally feasible and economically sound when combined with SMA. We would like to emphasise that while QALYs are a useful metric, rare-disease screening programmes deliver transformational value for children, families and society. The ISE showed that early detection led to markedly higher survival and quality of life for both children and families affected by rare conditions, whereas no screening was associated with a longer diagnostic odyssey and prolonged hospitalisation in intensive-care units. It is important to consider whether the model fully captures the 'opportunity cost', and explicitly how many babies might be adversely affected while decisions are paused. Further, SCID is considered ultra-rare in line with the estimated prevalence of 1 in 53,000 births (NHSE pp11). We would like to flag that since 1 April 2025, NICE's Highly Specialised Technology (HST) programme allows a higher willingness-to-pay threshold of up to £300,000 per QALY for qualifying ultra-rare conditions, up from the standard £30,000 per QALY.

- The cost per newborn was estimated to be £7.48 per newborn (p.7).
- The ScHARR report found that screening for SCID alone was above the usual threshold, with an ICER of about £87,800 per QALY, but became highly cost-effective when delivered together with SMA screening (pp61-62).
- When laboratory costs were shared with SMA, the cost per QALY fell to £4,409-£8,062, with a 97-98% probability of being cost-effective at the current NICE threshold.

In its November meeting, it would therefore be helpful if the UK NSC explicitly references the affordability challenge for rare conditions and the justification for applying broader criteria (severity, equity, avoidable death), such as via a Health Equity Audit to understand the potential impact of an extension to the ISE.

4. It is not clear what further information a prolonged ISE could realistically gather. The existing evaluation has already gathered evidence to inform feasibility, acceptability, vaccine safety, cost-effectiveness and laboratory logistics required to move forward.

- Parents overwhelmingly supported screening (NHSE report p16), and anxiety following false-positive results diminished by the child's first birthday (pp61-63).
- Demands on the workforce in laboratory and immunology teams (pp8-9,70) are unlikely to be unique to the ISE for SCID and so non-approval of a newborn screening programme for a rare condition would not address these broader workforce challenges.
- Concerns about BCG and SCID screening have been addressed through a straightforward operational change. International experience from Taiwan, Saudi Arabia and Singapore shows that programmes can safely coordinate SCID screening with neonatal BCG by modestly adjusting timing or, in specific contexts, by maintaining BCG at birth with careful monitoring. The balance of evidence indicates that this should not be a barrier to prompt approval and roll out of SCID screening.
- It is our understanding that uncertainty about long-term outcomes for babies with non-SCID T-cell lymphopenia cannot be resolved through another limited evaluation and would be better studied through national monitoring once screening is implemented.

5. Continued deferral in the UK risks widening the gap between the UK and comparable nations and undermining public confidence in the newborn screening programme. We would like to query the extent to which the evaluation situates UK performance in the global context. Internationally, SCID screening has already been introduced in at least 23 countries, including the US (2010), Taiwan (2012), New Zealand (2017), Norway (January 2018), Switzerland (January 2019), Germany and Sweden (August 2019), Denmark (February 2020), Austria and the Netherlands (2021).

A number of these countries introduced SCID screening prior to or around 2020, and some use the same assay to test for SMA. Since then, in 2024-25, Portugal, France, Spain and Italy followed suit. Further afield, it is also worth mentioning Canada, Ukraine, Israel, Lebanon, Taiwan, Hong Kong and Singapore have implemented SCID screening, while others such as Brazil and Malaysia, are researching how to do the same.

In particular, we'd like to note:

- Czechia piloted SCID screening from 2022-2023 before incorporating it into the national programme in 2024.
- As mentioned in our report *Time to Decide*, New Zealand implemented SCID screening without a pilot, as stakeholders perceived further evidence gathering unnecessary.
- In France, the screening pilot for SCID for over 190,000 babies (DEPISTREC) reported similar findings in 2019 – that the test was estimated to cost €4.7-8.15 per newborn and the PPV was ~4.7% (3 of 62). The French Health Authority (HAS) has since made a positive recommendation, and SCID screening was implemented on 1 September 2025.
- In 2023, the Republic of Ireland's NSAC recommendations to include both SCID and SMA in the national newborn screening programme were approved.

6. The community's perspective underscores why screening for SCID is so urgent.
It is noteworthy that the ISE report concludes that, although some families experienced temporary stress from receiving a false positive screening result, these concerns had mostly resolved by the child's first birthday, and despite these experiences, 'the overwhelming view' was that parents recommended that SCID screening be included in a national programme (NHSE pp62-63). This is important to highlight, as the 'harm' of a false-positive result is often referred to as one of the reasons for non-recommendation for screening. In the case of SCID, it is our view that this is not proportionate to the harm resulting from being diagnosed with a life-limiting condition too late. Should the ISE be extended, some families will continue to be denied screening, and for many of those families, their children will not reach their first birthday.

- Parents overwhelmingly supported screening (NHSE report p16), and anxiety following false-positive results diminished by the child's first birthday (pp61-63).
- Babies born in areas that were offered screening were referred to a SCID centre at an average of 21 days old. For those who were not, this ranged 90-173 days (NHSE, p46).
- Time to definitive treatment was 79 days for screened babies and 189 days for clinically diagnosed babies. This difference can determine survival.

7. We have a clear opportunity to learn from the delays surrounding start of an ISE for SMA.
The UK NSC first reviewed SMA screening in 2018 and recommended an ISE in 2023, which has not yet started, and this delay is now being cited as a reason to extend the ISE for SCID. During this period, children continued to be diagnosed only after symptoms appeared, despite the availability of disease-modifying therapies. In our report, *Time to Decide* (July 2025), we highlighted SMA and SCID as examples of how the current one-condition-at-a-time approach has led to unacceptable delays in access to newborn screening.

To demonstrate the impact of a potential delay for SCID, we want to share with you two stories from one of our member organisations, Immunodeficiency UK: Charlie's story, as the first child diagnosed with SCID in the UK via the ISE, and the story of Scott's family, whose first child did not receive screening for SCID and sadly later passed away (prior to the UK NSC ISE).

Scott's story (did not receive screening)	Charlie's story (received screening)
'At around eight weeks old, Scott developed a cough that didn't improve, so we took him to the doctor's surgery to seek further advice…Unfortunately, the infections, not picked up earlier, had already taken hold of Scott's fragile body. Despite the excellent care he received from the team in Newcastle, he passed away a few weeks later, at the tender age of seven months... Following Scott's death, our family underwent genetic testing… Aware of our family history of SCID, this time, we were offered a simple blood test for each child at birth. This simple life-saving test confirmed that our third son, Rhys, was SCID positive, and we were immediately transferred to the Bubble Unit at Newcastle RVI, where he was kept in a sterile and safe environment until he received a successful sibling matched bone marrow transplant at approximately five weeks old… We are eternally grateful to our firstborn, Scott, for highlighting this condition in our family, without whom we might not have Rhys or my nephew, who was also diagnosed at birth due to our family history and who, I'm happy to report, is also thriving…I can't stress how crucial early diagnosis of SCID is to improve the life outcomes of infants born with this condition. That is why adoption of a UK-wide newborn screening programme for SCID is imperative.'	'Charlie had blood taken and we went home to wait for news. The SCID diagnosis was confirmed later that day and we learned that Charlie would need treatment as soon as possible. We spoke to the hospital team and the quest to find Charlie a donor for a stem cell transplant began immediately…By the time Charlie turned seven months old, his immune system was working well and all social restrictions could be lifted. We were able to take him to baby classes and to visit friends and family, and he could play happily in close contact with Alfie…Today, Charlie is almost three and lives a very happy and healthy life, completely unaware of everything he went through. He has been attending nursery since he was 18 months old, and is thriving socially and developmentally. We learned that, normally, babies in the UK would get very poorly before finding out that SCID was the reason why, and that in a lot of cases the baby would die. Therefore, I feel so grateful every single day that our area of the country was involved in the pilot SCID newborn screening project when Charlie was born. I would hate to know what Charlie's experience might have been if he hadn't had the test.'

It is our position that the ISE for SCID has fulfilled its intended purpose, and a UK NSC recommendation to offer all newborns the same opportunity is now urgent. SCID screening has been proven to be clinically effective, safe, acceptable to families and highly cost-effective when implemented alongside SMA. The reports from this review do not clearly justify further evidence gathering through an extension, which would only prolong the existing postcode lottery for families affected by SCID in England. Extending the ISE to 2030 would mean almost 20 years since SCID screening was first proposed to the UK NSC (in 2011) and longer since its initial review (in 2003), continuing to deny equitable access to affected newborns. We therefore urge the UK NSC to move to a full national recommendation for combined SCID and SMA screening, with ongoing data collection through national implementation rather than a further extended evaluation.

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