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Assessing the cost-effectiveness of screening for Severe Combined Immunodeficiency (SCID) in the newborn bloodspot screening programme:

NHS SCID Screening Evaluation in England

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Hosted by the UK Department of Health and Social Care.

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Ethics statement

The economic analysis is based upon secondary analysis of research data. Whilst formal ethics approval was not required this position was approved under a University of Sheffield ethics self-assessment process (reference 043264).

Executive Summary

Introduction

The aim of this health economic evaluation is to provide estimates of the cost effectiveness of screening newborns for severe combined immunodeficiency (SCID), to support a final decision by the UK National Screening Committee on the inclusion this condition within the NHS Newborn Bloodspot Screening Programme following the NHS SCID Screening Evaluation.

The objectives are to update the health economic model that informed UK NSC SCID decision making in 2016/17 with evidence from the NHS SCID Evaluation, the parallel SCID outcomes research and published literature on SCID. The full reports detailing the NHS SCID Evaluation and the SCID outcomes research are reported separately.(1, 2) Model outputs include incremental health benefits and costs of screening newborns for SCID compared to the current practice of presentation and diagnosis through SCID symptoms and through investigation following SCID family history.

Methods

The SCID Model is an update of the model used by the UK NSC to inform its recommendation to establish the SCID Screening Evaluation in 2016/17. The Model compares NBS for SCID against the pathway for these babies without screening. The Model uses a decision-tree framework to simulate short-term pathways, together with a lifetable approach with annual intervals to assess long term outcomes. The Model incorporates costs and health outcomes associated with the screening pathway, providing a structure to analyse the trade-offs between early detection, intervention, and potential long-term cost savings. The Model is a cohort model and parameter uncertainty is characterised, described and analysed through Monte Carlo sampling. The Model adopts a lifetime horizon and the analysis is conducted from the NHS perspective.

The key Model updates include:

- incorporation of parental health-related quality-of-life (HRQoL) impacts associated with false positive screening and non-SCID TCL results,
- incorporation of parental HRQoL impacts resulting from bereavement,
- improved modelling of non-SCID T-cell lymphopenia (TCL), including changes to categories considered and incorporation of some cost and outcome implications,
- updated assessment of SCID survival and HRQoL outcomes,
- updated assessment of SCID secondary care management costs.

There are three primary sources of data for the health economic model; the NHS SCID Evaluation (including the prospective SCID data collection, the retrospective SCID cohort from Great Ormond Street Hospital for Children NHS Foundation Trust (GOSH) and Newcastle Upon Tyne Hospitals NHS Foundation trust (NUTH) and routine HES and ONS data), data from the parallel SCID Outcomes Research study and published and grey literature.

Birth prevalence for the four Nations is estimated from the retrospective NUTH, GOSH cohort data from collected between 2010 and 2020. The UK birth prevalence (1.89 per 100000) is used within the

Model. The proportion of SCID patients identified through family history in the absence of screening is 25% (37/146) also estimated from this cohort.

The SCID screening programme protocol and detection characteristics are taken from the SCID Evaluation. The Evaluation analysis has investigated different screen detection algorithms, including varying test result cut-off thresholds; the duplicates threshold (A), the referral threshold (B) and a threshold for immediate referral in blood spots taken from premature babies who are in neonatal intensive care (C). The baseline economic analysis implements the algorithm designed to minimise the number of referrals in extremely premature babies whilst ensuring no true SCIDs are missed (Thresholds: A = 10, B = 6, C = 1.08) and uses the patient final disposition and benefit data generated by the Diagnostic Reference Group of the SCID Evaluation Oversight team.

The primary definitive treatments (DTs) for SCID are haematopoietic stem cell transplantation (HSCT), with gene therapy (GT) potentially available for patients with adenosine deaminase-deficient severe combined immunodeficiency ADA-SCID and X-linked SCID and thymic transplant (TT) appropriate for patients with athymic SCID. The model estimates survival for SCID patients differentiated by route of presentation, that is through symptomatic, family history or screen detection. The model uses evidence on survival up to 10 years from the retrospective data for SCID patients managed at NUTH and GOSH identified between 2010 and 2020 (followed up until 2024) together with survival up to 1 year for SCID patients detected by screening during the Evaluation. Post 10-year mortality rates are based on the literature.(3)

The quality of life of SCID patients is estimated from doctoral research undertaken at the University of Newcastle by Intan Juliana Abd Hamid who investigated the clinical, immunological and psycho-social outcomes in SCID patients who underwent HSCT(4) together with HrQoL mapping algorithms from the published literature.(5) Parental quality of life impacts of SCID screening results were taken from the research study undertaken in parallel with the Evaluation that explored the impact of screening on parents and health professionals.(2) Parental bereavement HrQoL impacts were taken from a UK research study.(6)

The laboratory costs of screening, costs of confirmation and diagnosis were estimated from the SCID Evaluation. SCID secondary care management costs were estimated from HES activity recorded for the retrospective and prospective SCID Evaluation cohort and differentiated by presentation route. The scope of this activity data includes all secondary care activity in England, specifically including activity beyond GOSH and NUTH. This means that impacts of screening in avoiding the diagnostic odyssey of symptomatically detected SCID patients is included within the analysis.

Probabilistic sensitivity analysis is used to estimate the baseline economic results. Scenario analyses include consideration of SCID birth prevalence, discounting rates, assumptions concerning the use of enzyme replacement therapy, the apportionment of screening costs between SCID and spinal muscular atrophy (SMA) and assumptions regarding the estimation of screen detection survival.

Results

Screening is estimated to provide early detection for between 11 and 15 cases of SCID per year compared to 3 (95% CI: 2, 4) babies being detected early by family history without screening. It is predicted that 0.3 (95% CI: 0, 0.8) SCID cases may be missed by screening, or one case missed every 3 (95% CI: 1, 50) years.

However, screening with the IIVD SCID technology, using the optimised Evaluation algorithm (A3) is predicted to result in between 35 and 68 babies receiving a false positive result annually that would be identified at flow cytometry.

A further 65 patients (29, 116) will be expected to receive a non-SCID TCL result and require further follow-up and investigation. Of these babies 15 (5, 30) might be expected to be diagnosed with syndromes or non-SCID TCL secondary to other conditions that might have been expected to arise symptomatically in the absence of screening.

Four (1, 11) of the babies investigated for non-SCID TCL might be expected to have persistent idiopathic non-SCID TCL. A similar number of babies 4 (1, 11) might be expected to resolve spontaneously during follow-up. If follow-up investigation in practice is similar to that undertaken within the Evaluation, then it is estimated that approximately 41 (22, 65) babies and their parents will have some level of investigation triggered by screening that is inconclusive. It is estimated that in 18 (9, 28) of these cases the baby will have died shortly after birth.

Screening is expected to reduce the average age of definitive treatment from 10 months for those who would have otherwise been diagnosed symptomatically to approximately 4 months. Improved management following early detection is estimated to lead to one (1, 2) avoided SCID deaths at 12 months of age per annual cohort and between 1 to 3 avoided deaths at 10 years of age.

Screening is predicted to deliver 55 (5, 97) additional quality adjusted life years (QALYs) discounted over the lifetime of an annual UK SCID cohort. Parental quality of life impacts included within the model include the adverse effects of receiving a false positive result from the baby's SCID screening test, a minimal proxy assessment of uncertainties associated with a subset of non-SCID TCL results, together with an assessment of parental bereavement impacts following infant death. The total QALY impact of screening on an annual cohort of parents is a loss of 1 (loss 9, gain 4) QALYs, indicating that on average the total QALYs lost through diagnostic uncertainty consequent on screening are greater than the QALYs gained through avoided bereavement, reflecting the larger number of parents affected.

The incremental costs of screening and subsequent diagnostic investigations are estimated at approximately £5.3m per year. Early detection and improved management of an annual cohort of SCID patients is estimated to save approximately £419k (£102k, £749k) in the first year and an additional £38k (-£369k, £438k) discounted over the lifetime of the annual cohort. The incremental total discounted cost of screening is therefore estimated at £4.8m (£4.3m, £5.4m) per year.

The cost effectiveness of screening for SCID compared to no screening is estimated at £87,813 per QALY gained. The UK 2022 population net monetary benefit of screening at a cost effectiveness threshold of £30,000 per QALY is -£3.2m (-£4.5m, -£2.0). The full economic report describes a range of sensitivity analyses.

The primary scenario analysis that has the potential to impact on the economics of screening for SCID is the apportionment of laboratory test costs of screening between SCID and SMA. Both the IIVD and Revvity screening technologies assessed in the Evaluation have the capability and functionality to detect both SCID and SMA. The apportionment of the fixed and operating laboratory costs between the two conditions therefore has the potential to impact on the economics of screening for either. The baseline economic analysis assumes that all the laboratory costs of screening are allocated to SCID. If screening is undertaken for both SMA and SCID then apportionment of the laboratory costs of screening needs to be considered.

Sensitivity analyses examine two alternative approaches to apportioning the cost of the screening. Firstly, the marginal impact of screening for SCID+SMA compared to screening for SMA alone is considered, that is 10% of the laboratory cost of screening. Secondly, apportioning of costs according to the relative birth prevalence of the two conditions is considered. The cost effectiveness of screening for SCID in these two scenarios are estimated at £4,409 and £8,062 per QALY gained respectively and the probability that it is cost effective at a threshold of £30,000 is 98% and 97% respectively.

Conclusions

Taken on its own the cost effectiveness of screening for SCID compared to not screening is in the order of £80-90k per QALY gained when costs and QALYS are discounted at 3.5%. This is higher than economic thresholds typically implemented in the UK. Furthermore, the combined parametric uncertainty captured in the Model is such that the 95% confidence interval for the incremental net monetary benefit of screening is wholly negative. Whilst approaches to discounting have the potential to impact on the economics of screening for SCID, the above conclusions are robust to all the discounting scenarios considered in this report.

The cost effectiveness of screening for SCID is highly dependent on the birth prevalence, with the economics of screening deteriorating with lower levels of birth prevalence. There are two issues arising. Firstly, the SCID birth prevalence within the period of the Evaluation was lower than the average used in the model. If this lower birth prevalence is evidence of a trend towards lower levels of SCID then screening will become less cost effective than estimated here. Secondly, there is evidence of high levels of geographical (as a proxy for other factors) variation in the birth prevalence of SCID. This report demonstrates that the economics of screening for SCID may vary between the four UK Nations, with Wales, Scotland and Northern Ireland all demonstrating lower SCID birth prevalence than England.

The latest generation of SCID screening technologies, including the IIVD and Revvity products included within the SCID Evaluation, also provide the facility to screen for SMA within the same screening laboratory process. How the laboratory costs of screening are apportioned between the two rare conditions has a crucial impact on the economics of screening for SCID. This analysis has examined two approaches to apporting the cost of screening. Firstly, the minimum marginal cost of screening for SCID + SMA compared to screening for SMA alone and secondly according to the relative birth prevalence of the two conditions. These analyses demonstrate a major impact on the economics of screening for SCID, with an average cost effectiveness of better than £10,000 per QALY gained in both cases.

This modelling study has identified and included the parental impacts of screening for SCID. The SCID Evaluation and associated outcomes research study have been successful in addressing uncertainties in the number and impact of false positive results generated by SCID screening that were an issue in the previous UK NSC consideration. The new generation IIVD test implemented in the SCID Evaluation gives rise to fewer false positives than the previous SCID screening technology. The SCID outcomes research identified and estimated the negative impact of these babies' false positives results on parental quality of life.

There are significant remaining uncertainties in the performance of the SCID screening technologies with regard to the number of incidental, non-SCID TCL and inconclusive findings that are generated. However, given that the parental QALY impacts identified are an order of magnitude smaller than the

direct QALY benefits to babies, it is unlikely that these uncertainties will impact on the economics of screening. Thus, while managing and minimising incidental findings from SCID screening may be an area for further research and screening development, this is not primarily an economic issue.

Contents

1 Introduction

1.1 Background

In 2016/17 the UK National Screening Committee (UK NSC) considered screening for severe combined immunodeficiency (SCID) within the NHS Newborn Bloodspot Screening Programme. In order to resolve key uncertainties regarding implementation and cost effectiveness the UK NSC recommended that an evaluation of screening for SCID should be undertaken. Public Health England and NHSE jointly established the SCID Screening Evaluation, running from 01 September 2020 to 29 February 2024.

A health economic model of screening for SCID was developed by SCHARR as part of the evidence prepared to support to the UK NSC in its 2016/17 deliberation.(7) This report describes the updating of the original SCID screening model to include evidence that has emerged since 2016, together with evidence from the NHS SCID Screening Evaluation and SCID research commissioned by PHE on SCID outcomes.

1.2 SCID and newborn screening

Severe combined immunodeficiency (SCID) is the name for a group of very rare genetic disorders. There are more than 10 genetic types of SCID, but all are characterised by a severe defect in T cell production and function. Infants born with SCID have weakened immune systems and are vulnerable to infections, which can be serious or even life threatening. Left untreated, infants with SCID usually die within the first year of life, though early detection and treatment can improve survival. The primary treatment option for SCID is haematopoietic stem cell transplant (HSCT), though gene therapy (GT) and thymic transplant (TT) are appropriate certain subtypes of SCID and enzyme replacement therapy (ERT) has a role in therapy. Newborn screening for SCID holds out the prospect of improving early detection of SCID and thereby improving management and outcomes.

1.3 Aims and objectives of the SCID Model

The aim of the project is to provide estimates of the cost effectiveness of screening for SCID, to support a final decision by the UK National Screening Committee on the inclusion of this condition within the NHS Newborn Bloodspot Screening Programme following the NHS SCID Screening Evaluation.

The objectives of the economic work programme are:

1. Update the existing ScHARR SCID screening cost-effectiveness model with evidence from:
   - the NHS SCID Evaluation,
   - SCID outcomes screening research,
   - Published and grey literature on international SCID screening programmes and pilots and
   - Published literature relating to SCID screening economics, including for instance other economic evaluations of SCID, long term SCID outcomes and costs.
2. Expand the scope of the pre-existing SCHARR cost effectiveness model to include parental outcomes and false positive impacts.
3. Produce a report detailing the cost effectiveness of including screening for SCID compared to the current situation of no SCID screening within the existing blood spot screening programme.

2 Economic evidence for SCID screening published since the previous SCHARR economic modelling

Since 2016, besides the original publication of the SCHARR SCID screening model,(7) there have been seven studies reporting on the economics of SCID and SCID screening.(8-14) Study details, including scope, methods and data sources used are included in Appendix 1.

The Ding et al study reports an economic modelling exercise for Washington State in the US.(8) In the Netherlands, 2019, an early decision tree model was developed that examined the potential cost effectiveness of screening for SCID in a modelled population. (9) This model was updated in 2021 following the Netherlands SCID screening pilot.(10) In Australia, Shih has published two health economic analyses based upon modelled populations, one looking at the cost effectiveness of SCID alone(11) and the second looking at the combined cost effectiveness of screening jointly for SCID and SMA.(12) Thomas et al have reported a cost analysis of SCID treatment in France based upon a cohort of SCID patients identified between 2014 and 2017, note that comparative cost effectiveness was outside the scope of this study.(13) The only UK SCID study is the publication of an Evidence Review Group's assessment of an economic submission to NICE for a gene therapy treatment for ADA-SCID that is itself only published in redacted form on the NICE website.(14)

The US study by Ding, estimated the cost effectiveness of screening to be $35,300 per life year gained.(8) The study by Shih(11) estimated the ICER for SCID screening in Australia to be US$33,600 per QALY gained over a 60 year time horizon with 3% discounting.(11) The original Dutch study estimate the ICER to be €33,400 per QALY gained with a lifetime horizon and 3% discounting(9) however, this increased to €41,600 per QALY gained when updated estimates of the costs of the screening test and subsequent diagnostics was included following the Dutch evaluation of SCID screening in three provinces.(10)

3 Health economic modelling methods

3.1 Overview and Model structure

A decision analytic model, hereafter referred to as the SCID Model, was developed to estimate the health and economic impact of including SCID in the NHS Newborn Blood Spot Screening Programme. The Model aims to estimate the incremental health benefits and costs of screening newborns for SCID compared to the current practice of presentation and diagnosis through SCID symptoms and through investigation following SCID family history.

The SCID Model was developed based upon a previously published model.(7) The Model compares NBS for SCID against the pathway without screening. The Model employs a decision-tree framework to simulate short-term pathways and outcomes associated with screening, diagnosis, and treatment, as well as long-term outcomes post-screening to assess the clinical impact of screening strategies. The Model incorporates costs and health outcomes associated with the screening pathway, providing a structure to analyse the trade-offs between early detection, intervention, and potential long-term

cost savings. The Model is a cohort model and adopts a lifetime perspective, outcomes are assessed via a lifetable approach with annual intervals. The economic evaluation is conducted from the NHS perspective.

Compared with previously published models in SCID screening, this updated version includes the following key refinements:

- Updated modelling of non-SCID T-cell lymphopenia (TCL), including changes to categories considered and incorporation of some cost and outcome implications.
- Incorporation of parental health-related quality-of-life (HRQoL) impacts associated with false positive screening and non-SCID TCL results.
- Incorporation of parental HRQoL impacts resulting from bereavement.
- Updated assessment of survival outcomes based upon retrospective data from NUTH and GOSH, SCID Evaluation data, HES data and ONS mortality data.
- Updated assessment of SCID secondary care management costs, through analyses of retrospective data and HES data.

Figure 1 illustrates the structure of the decision-tree model, including 11 health states (S1 to S11). In the absence of screening, SCID cases are diagnosed either due to family history (S7) or through symptomatic presentation (S8). In addition, a proportion of SCID cases may remain undetected in the absence of screening, referred to as missed SCID (S9). In the screening arm SCID cases (S1) are detected and diagnosed based on the sensitivity of the screening test. Among false-negative SCID cases, it is assumed that the same proportion of SCID cases will be detected through a family history as in the non-screening arm (S4), while others are diagnosed through symptomatic presentation (S5).

Throughout the model, SCID cases diagnosed via newborn screening or family history are considered early detection (S1, S4, S7), while cases identified symptomatically are considered late detection (S5, S8). Missed SCID cases (S9) result in mortality. All health states representing detected SCID (S1, S4, S5, S7, S8) share the same diagnostic and treatment pathways, as depicted in Figure 2. The Model is implemented with the structure to facilitate detailed modelling of SCID subtypes. For some cases of ADA-SCID and X-linked SCID where matched family donors are unavailable, gene therapy (GT) is utilised. ADA-SCID and X-linked SCID with matched family donors, and other non-athymic SCID cases undergo haematopoietic stem cell transplantation (HSCT), while all athymic SCID cases undergo thymus transplantation (TT). Except for some cost aspects of GT in ADA SCID, the SCID subtype components of the Model are, due to constraints in data availability, not differentiated within the model and are assumed to be as for generic SCID. Mortality outcomes for SCID cases are assessed within the Model differentiated by early and late detection. The modelling of short and long-term survival is described further in the Survival section.

Babies who receive a false positive result (S2) incur no health disbenefit nor further costs in the Model. However, parents of babies with a false positive result incur a one-off reduction in parental health utility, this is based upon the results of the screening outcomes research study undertaken in parallel to the Evaluation.(2)

For other conditions identified by screening, classified as non-SCID TCL, the Model includes various subtypes as outlined in Figure 3 that correspond with the classifications of SCID screen positive results defined in the Evaluation Final Report.(1) The Model does not separate out extreme premature babies who are in neonatal intensive care at the time of screening, other than through effects of the screening algorithm, this is in accordance with the approach taken in the Evaluation. The Model incorporates marginal short-term impacts on follow-up and diagnostic costs and parental

impacts resulting from screening for these non-SCID TCL conditions. Non-SCID TCL impacts are estimated as marginal compared to no screening. Potential long-term costs and health outcomes associated with non-SCID TCL are not included in the Model. To maintain model consistency and symmetry, these conditions are represented in the no-screening arm (S10), but no associated costs or health outcomes are included.

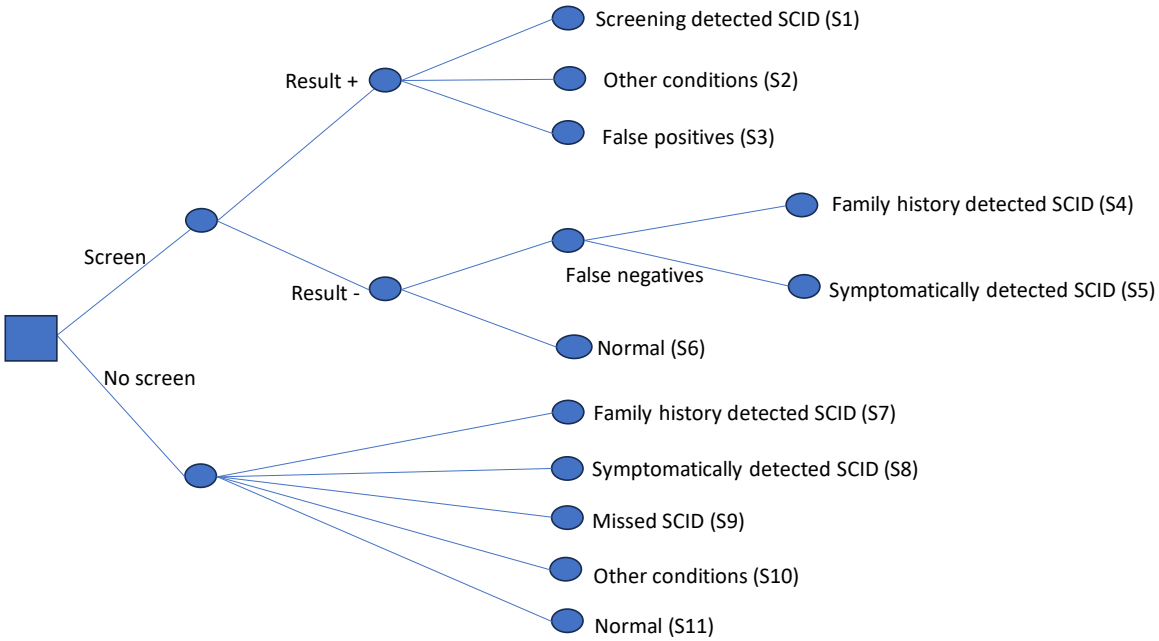


Figure 1 SCID Model decision tree structure

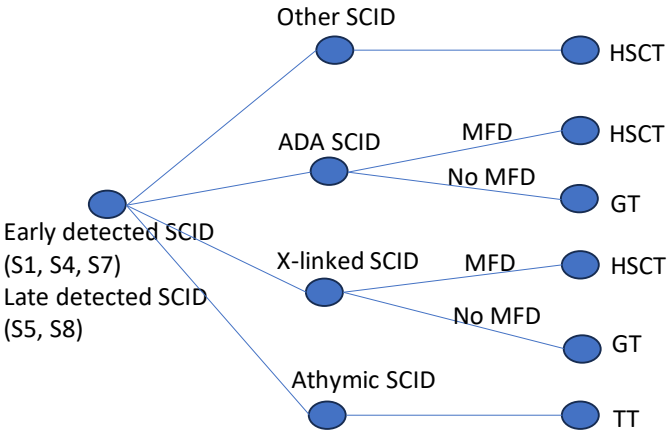


Figure 2 Detected SCID types

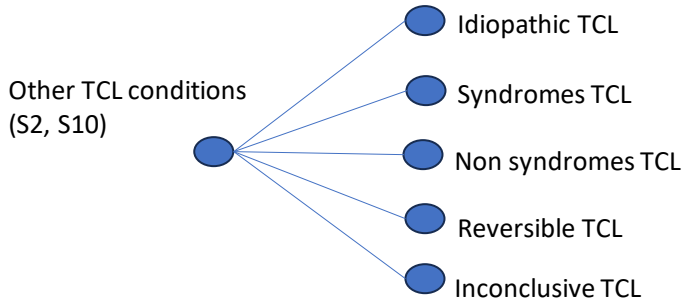


Figure 3 Non-SCID TCL conditions detected by screening

3.2 Overview of health economic model parameterisation

There are three primary sources of data for the health economic model: the NHS SCID Evaluation, the parallel SCID Outcomes Research(2) and published and grey literature.

SCHARR was not directly involved in the data collection within the SCID Evaluation but received data from the NHSE Evaluation team. Data flows to and within SCHARR for the economic evaluation were established in accordance with The University of Sheffield's Information Governance and Research Data Management policies. A data flow diagram for the SCID Evaluation (Personal communication R Knowles 12/01/24) is included in Figure 4.

The SCHARR team was involved throughout the Evaluation in ensuring data flows were established and operated adequately and that data was as far as possible fit for the purposes of the economic evaluation. The NHS SCID Evaluation collected data from four sources:

1. Prospective data from the SCID Evaluation including:
    a. Data from the laboratories and associated immunology centres for their catchment population,
    b. Data from the two SCID clinical centres at GOSH and NUTH on both screened and non-screened SCID patients. This included screen detected patients, symptomatically detected patients, and family history detected patients,
    c. Data from the Diagnostic Review Group of the SCID Oversight Board regarding final patient final dispositions and benefits and
    d. HES data on secondary care activity for patients with a positive SCID screening result.
2. Retrospective data collected as part of the SCID Evaluation including:
    a. from the two clinical centres at GOSH and NUTH. This included symptomatic and family history detected patients and
    b. national HES and ONS mortality data on secondary care activity and outcomes for the retrospective SCID cohort.

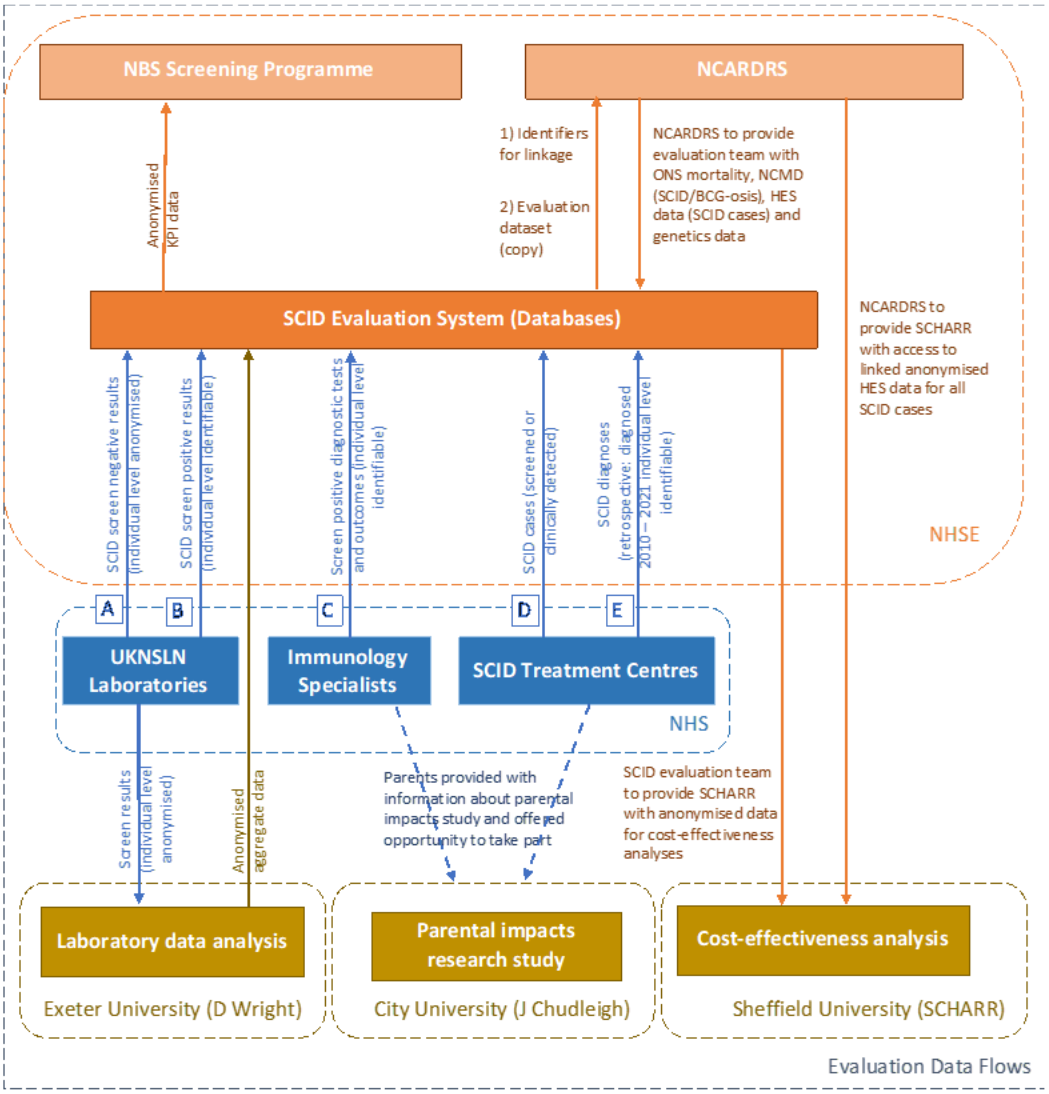


Figure 4 SCID Evaluation data flow diagram

Key to the primary data collection

A and B: Data from screening laboratories – identifiable individual-level data from screen positive cases; individual-level anonymised data from screen negative cases

C: Data from immunologists responsible for screen positive cases – identifiable individual level data on screen positive cases (includes diagnostic testing and outcome data on those with immunological diagnoses)

D and E: Data from specialist centres – identifiable individual-level data from SCID cases identified during the evaluation and anonymised individual-level data from 2010-2021 prior to the evaluation ('retrospective')

Abbreviations: NBS = Newborn Blood Spot; SCID = severe combined immunodeficiency; BCG-osis = disseminated BCG vaccination; NHSE = NHS England; ONS Office for National Statistics; HES = hospital episode statistics; NCMD = National Child Mortality Database; NCARDRS = National Congenital Anomaly and Rare Disease Registration Service; SCHARR = Sheffield Centre for Health and Related Research; UKNSLN = UK National Screening Laboratory Network; KPI = key performance indicators

The table below identifies how model parameters will be sourced for the health economic model.

Table 1 Overview of model parameter sources

Parameter set \ Data source	NHS SCID Evaluation			SCID Outcomes Research	Hamid doctoral research	Published and grey literature
	Prospective	Retrospective	HES and ONS data			
Epidemiology of SCID		√				√
Screening test characteristics	√					√
SCID pathway and management	√					√
SCID mortality	√	√	√			
SCID resource usage, cost	√	√	√			
SCID patient, QoL outcomes		√			√	√
Child and parent QoL outcomes, non-SCID TCL	√			√		
Child and parent outcomes, false positives	√			√		
Parental QoL bereavement outcomes						√

3.3 Epidemiology

Birth prevalence of SCID in the UK is estimated from the SCID cases known to the two SCID specialist centres, Great Ormond Street Hospital for Children NHS Foundation Trust (GOSH) and Newcastle Upon Tyne Hospitals NHS Foundation trust (NUTH) and the births recorded in ONS statistics between 2010 and 2020. The SCID Evaluation Team investigated the potential occurrence of SCID cases with early death that may not have presented or been known to GOSH and NUTH, but no cases were identified.

The birth prevalence figures for the four nations and the UK are included in Table 2 and Figure 5. Whilst the average birth prevalence in each of Wales, Northern Ireland and Scotland are consistently lower than England these differences do not reach significance. The model provides the functionality to select birth prevalence from any of the four nations. The annual variation in the number of SCID cases in England is presented in Figure 6.

The birth prevalence is implemented as a Beta distribution and the model provides the functionality to generate outputs for the four nation and UK births in 2022, together with a standard 100,000 population cohort. For validation purposes the Model can also be run for the subset of the Evaluation cohort on which the test characteristics were based.

Table 2 UK Birth prevalence of SCID between 2010 and 2020

	England	Wales	Scotland	North Ireland	Total
Total births	**7,191,082**	**362,086**	**598,574**	**261,985**	**8,415,667**
Total SCID	**141**	**5**	**10**	**2**	**159**
Birth prevalence 2010-2020	**1.96E-05**	**1.38E-05**	**1.67E-05**	**7.63E-06**	**1.89E-05**

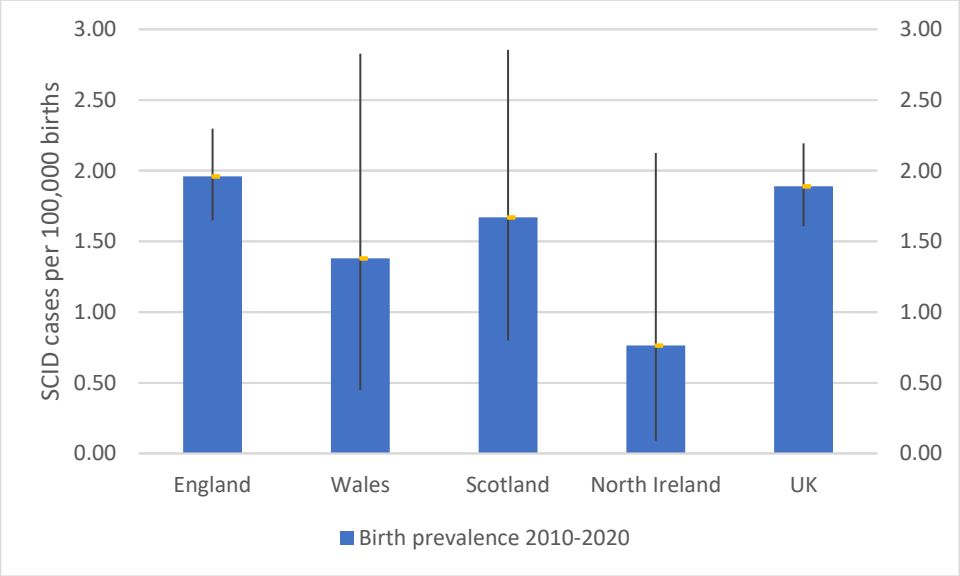


Figure 5 UK Birth prevalence of SCID

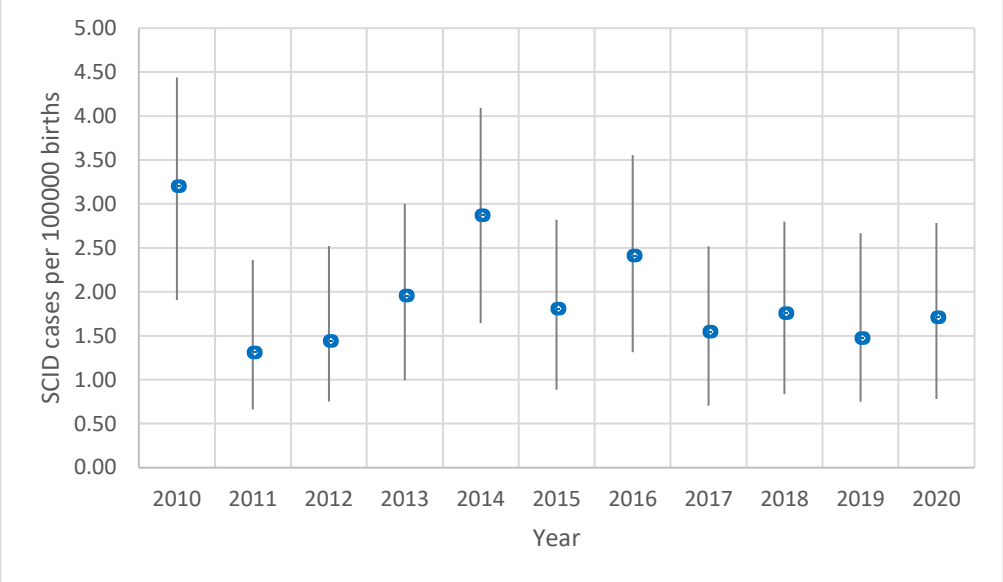


Figure 6 Annual variation in SCID birth prevalence 2010 to 2020 in England

In the absence of screening, babies with SCID either present symptomatically or, where the family is already known to the health service, through family history. The proportion of babies with SCID who are diagnosed through family history is estimated from the retrospective data from NUTH and GOSH between 2010 and 2020 and is 25% (37/146). The proportion of family history cases is implemented as a Beta distribution within the model.

3.4 Screening programme characteristics

Figure 7 presents the SCID screening process and the screening journey from the perspective of the parent. The screening process commences with the provision of information to the parent in the prenatal period (including consenting processes), following the birth of the baby a heel-prick bloodspot is taken and sent for processing at the laboratory. Negative test results are reported back to the parent and GP by the Child Health Information Services (CHIS). Positive screening tests are provided to parents by the clinical team via an initial telephone appointment, followed by a face-to-face appointment at which a further blood sample is taken for confirmatory testing including flow cytometry. The potential outcomes of confirmatory testing are described more fully in the Evaluation Final Report,(1) but could result in outcomes of true SCID, non-SCID T-cell lymphopenia (TCL) or false positive results (Note that CFSPID (Cystic Fibrosis Screen Positive, Inconclusive Diagnosis) is included here as this was a component of the SCID outcomes research study (2) from which the Figure is taken, though this is not relevant to the SCID Evaluation).

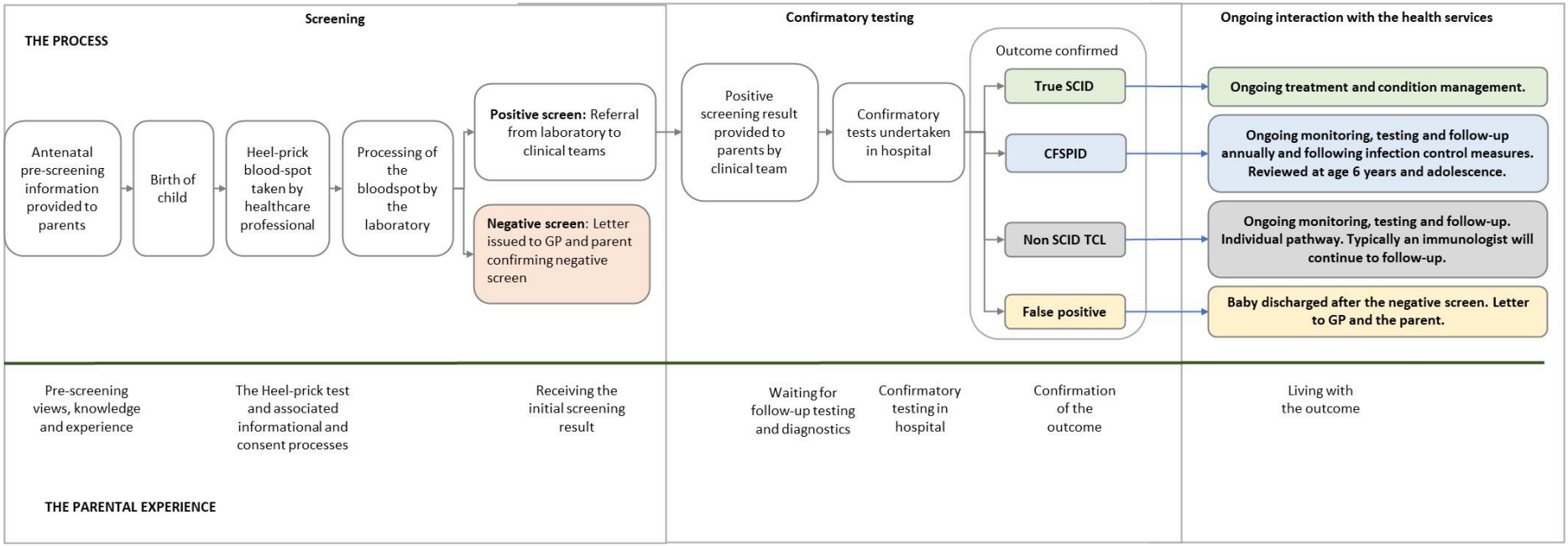


Figure 7 A summarised SCID screening journey

Replicated with permission from Table 9 of the report of the SCID outcomes research study(2)

Note CFSPID not relevant to the SCID Evaluation.

Three different laboratory technologies for SCID screening of bloodspots were implemented within the Evaluation:(1)

- SPOT-it™ TREC Screening kit from ImmunoIVD (IIVD), a real-time polymerase chain reaction (PCR) test implemented in the SCID Screening programme of The Netherlands. The marketed technology detects both SCID and Spinal Muscular Atrophy (SMA).
- EnLite™ Neonatal TREC Kit marketed by Perkin Elmer (now Revvity), test becoming obsolete and no longer marketed to new customers.
- EONIS Q™ a real-time PCR test marketed by Revvity. Note that this test was included in the Evaluation at a late date with a focus on determining feasibility. Similarly to the above, the technology detects both SCID and SMA.

This economic evaluation focuses on the IIVD SPOT-it™ TREC screening kit.

The performance of the screening technology in identifying SCID, non-SCID TCL and false positives results varies depending upon the specific screening algorithm implemented. Elements of the screening algorithm were modified during the evaluation, for example the use of geometric means rather than minimums in calculating test values from test pairs. The Evaluation analysis(1) investigated the impact of varying test result cut-off thresholds within the screening protocol; the duplicates threshold (A), the referral threshold (B) and a threshold for immediate referral in blood spots taken from premature babies who are in neonatal intensive care (C). The economic analysis investigates three different algorithms, described by different ABC threshold combinations. The different algorithms and performance in terms of repeats and referrals analysed within the Model are presented in Table 3, for further information on the algorithms considered and the referral performance analyses refer to the main Evaluation report and its Appendices.(1) Algorithm A1 identifies the greatest number of screen positive results and algorithm A3, with thresholds: A = 10, B = 6, C = 1.08, is designed to minimise the number of referrals in extremely premature babies whilst ensuring no true SCIDs are missed.

Table 3 IIVD Screening algorithm referral performance

Screening algorithm	**(A1) A = 12, B = 8, C = 4**	**(A2) A = 10, B = 6, C = 4**	**(A3) A = 10, B = 6, C = 1.08**
Population **Composition**	459,367 100.0%	459,367 100.0%	459,367 100.0%
Expected cases (1 in 50000)	9.19	9.19	9.19
Duplicates	1141 0.2%	1054 0.2%	1054 0.2%
Repeats	239 0.05%	235 0.05%	235 0.05%
Term repeats	25 0.01%	12 0.00%	37 0.01%
Referrals	112 0.02%	95 0.02%	85 0.02%
PPV	8.20% 1 in 12	9.56% 1 in 10	10.83% 1 in 9

The Diagnostic Review Group (DRG) of the Evaluation Oversight team reviewed records relating to babies with a screen positive result and classified them according to final Evaluation disposition and potential benefit. Nineteen DRG final disposition and six benefit categories were defined in the SCID Evaluation.(1) For the purposes of the economic evaluation these have been mapped onto eleven mutually exclusive Model condition categories, the details of this mapping are presented in Appendix 2. Algorithm performance in terms of false positive rates and non-SCID TCL condition categories are presented in Table 4. The baseline economic analysis implements algorithm A3 within the model.

Regarding sensitivity of the screening test, there was no evidence from the SCID Evaluation that any SCID patients were missed by screening either from SCID cases arising symptomatically in patients who had been screened with a negative screening results or through failure of the screening algorithm to detect cases of SCID. A systematic review of SCID screening commissioned by the UK NSC (15) identified four retrospective reports on the experience of SCID screening programmes internationally that reported sensitivity results.(16-19) Three of the studies (16-18) reported no false negative SCID cases and the largest study (19) of over 3.5 million babies screened identified 2 false negative cases. However, none of the four studies described give details of any standardised process for identifying or reporting cases of SCID missed by screening. The systematic review concludes that whilst there is evidence that TREC based screening technologies as implemented in screening programmes have a high sensitivity "it remains uncertain whether the apparent high sensitivity … is a reliable representation of the capture of SCID cases". (15) The Model uses a simple pooling of the above retrospective study results, with a 25% reduction of sample size, to account for potential issues around generalising between TREC tests and screening settings, together with the results from the SCID Evaluation to estimate screening test sensitivity, implemented as a Beta distribution Beta(73.75,1.5) with an mean sensitivity for SCID of 98.0% (93.9%, 99.9%).

Table 4 IIVD Screening algorithm performance for false positives and non-SCID TCL

Algorithm Analysis based upon 459,367 IIVD tests	A1 A = 12, B=8, C =4	A2 A = 10, B=6, C=4		A3 A = 10, B = 6, C = 1.08	
	n	n	%	n	%
Normal T-cell subset	48	44	92%	34	71%
Condition 1 - Idiopathic TCL - benefit	2	2	100%	2	100%
Condition 2 - Idiopathic TCL - unknown	2	1	50%	1	50%
Condition 3 - Syndromes TCL - benefit	6	5	83%	5	83%
Condition 4 - Syndromes TCL - no/neutral benefit	2	1	50%	1	50%
Condition 5 - Syndromes TCL - disbenefit	1	1	100%	1	100%
Condition 6 - Non syndromes TCL - benefit	1	1	100%	1	100%
Condition 7 - Non syndromes TCL - no/neutral benefit	2	2	100%	2	100%
Condition 8 - Non syndromes TCL - disbenefit	1	0	0%	0	0%
Condition 10 - Reversible TCL - disbenefit	3	3	100%	3	100%
Condition 11 - Inconclusive - alive - disbenefit	20	16	80%	16	80%
Condition 12 - Inconclusive - died - disbenefit	12	12	100%	12	100%
Grand Total	**100**	**88**	**88%**	**78**	**78%**
Subtotal - Benefit	9	8	89%	8	89%
Subtotal - No/neutral benefit	4	3	75%	3	75%
Subtotal - Unknown	2	1	50%	1	50%
Subtotal - Disbenefit	85	76	89%	66	78%

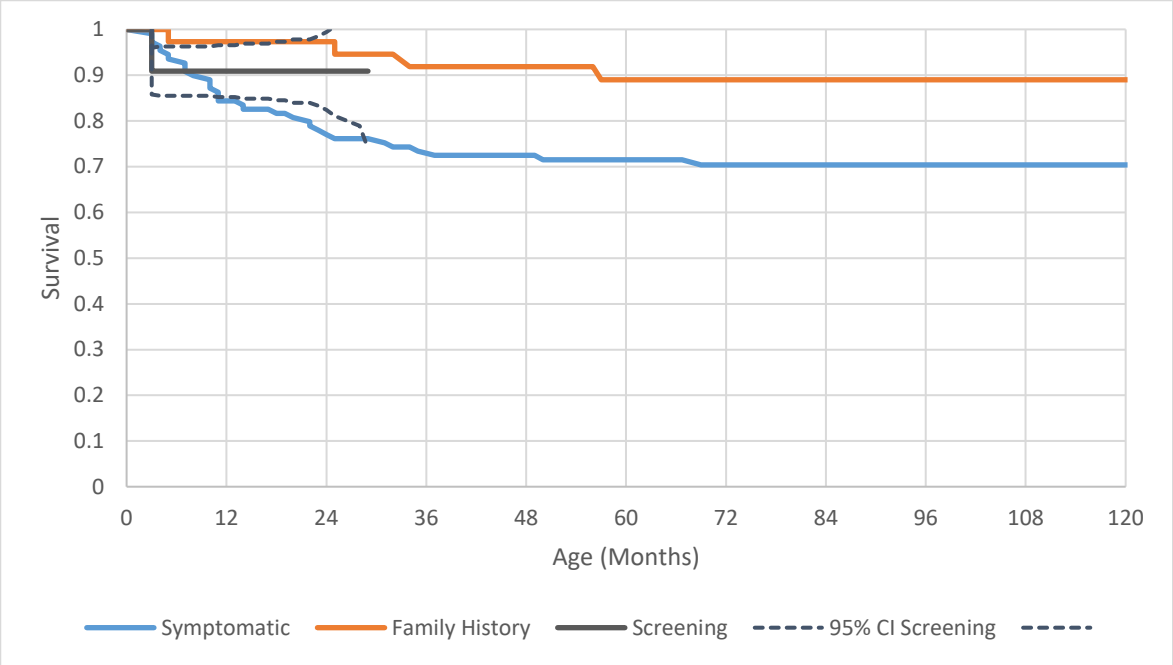
3.5 Treatments for SCID and modelling of survival.

The primary definitive treatments (DTs) for SCID are HSCT, with GT potentially available for patients with ADA-SCID and X-linked SCID and TT appropriate for patients with athymic SCID. The model estimates survival for SCID patients differentiated by route of presentation, that is through symptomatic, family history or screen detection. Whilst early diagnosis and treatment through family history or screen detection is likely to somewhat improve longer term outcomes, for instance due to the reduction in infections at the time of transplantation, the literature suggests the largest potential benefit of early detection is in the reduction in the short-term mortality. The model uses evidence on survival up to 10 years from the retrospective data for SCID patients managed at NUTH and GOSH identified between 2010 and 2020 (followed up until 2024) together with survival up to 2 years for SCID patients detected by screening during the Evaluation. Post 10-year mortality rates are based on the literature described below.

3.5.1 Short-term survival

The model has the provision to include a proportion of SCID cases that would remain undiagnosed in the absence of screening and for whom mortality would be 100%. An investigation of child mortality records undertaken during the period of the Evaluation identified no cases of SCID that had been missed in the presentation records of NUTH and GOSH. This proportion is therefore set to 0 in the Model.

Survival of family history and symptomatically diagnosed SCID patients up to 10 years is estimated from data obtained for consecutive patient cohorts from NUTH and GOSH between 2010 and 2020, followed up until 2024. Survival of screen detected patients identified within the SCID Evaluation is analysed up to 2 years. Interval Kaplan Meier survival analyses with variance estimated through the Greenwood method is undertaken, with follow up to 10 years and 2 years for the retrospective and screen detected cohorts respectively. Figure 8 presents the SCID survival up to 10 years for the retrospective cohort, with the 95% confidence intervals for the smaller (and more uncertain) Evaluation screening cohort presented.



At risk						
Months	0	12	24	36	48	120
Symptomatic	109	92	85	80	75	33
Family History	37	36	36	34	32	18
Screening	11	9	4	0	0	0

Figure 8 Survival of SCID patients in the Retrospective and Screening Evaluation cohorts

Annual mortality probabilities up to 10 years are estimated and implemented in the model as Beta distributions, Beta(a,b), with parameters, a and b, estimated from the mean and variance of Kaplan Meier interval probabilities, see Table 5. It is assumed that all pre transplant mortality, that is SCID patients who die before definitive treatment, occurs within 12 months of birth. The mortality in the first year is therefore subdivided into pre- and post-definitive treatment mortality.

In the Model, mortality for symptomatic and family history presentation is estimated directly from the retrospective SCID cohort. For screen detection, our prior assumption is that mortality would be as for family history detection, with a reduced equivalent sample size to account for the uncertainty attendant on this assumption. Up to 2 years, the baseline analysis for screen detection assumes a prior equivalent sample size of 50% of the original family history cohort, this assumption is investigated in sensitivity analyses. This prior screen detected mortality is updated in the light of the Evaluation data. This Bayesian approach reduces the high level of uncertainty in screening outcomes that would arise if we relied solely on the SCID Evaluation cohort as demonstrated in Figure 8. Table 5 presents the SCID mortality parameters up to 10 years of age estimated from the retrospective and Evaluation data. The impact of assuming that survival following screen detection is equivalent to the survival for family history detected SCID is included in sensitivity analyses.

Table 5 SCID mortality parameters up to 10 years

Interval Mortality	Late symptomatic detection			Early family history detection			Screen detection (Evaluation)			Screen detection (Model)		
	Death (a)	Survival (b)	%	Death (a)	Survival (b)	%	Death (a)	Survival (b)	%	Death (a)	Survival (b)	%
Pre-definitive treatment	2.81	73.84	3.7%	0.92	33.11	2.7%	0.33#	79.67#	0.4%	0.46	23.57	1.9%
Post definitive treatment to 12 months	9.14	64.70	12.4%	0.33#	79.67#	0.4%	0.74	6.69	9.9%	0.74	23.24	3.1%
12 to 24 months	5.90	71.63	7.6%	0.33#	79.67#	0.4%	0.33#	79.67#	0.4%	0.33*	79.67*	0.4%
24 to 36 months	4.37	69.92	5.9%	1.73	29.38	5.6%	N/A	N/A	N/A	1.73*	29.38*	5.6%
36 to 48 months	0.96	76.05	1.3%	0.33#	79.67#	0.4%	N/A	N/A	N/A	0.33*	79.67*	0.4%
48 to 120 months (annual)	1.75	386.3	0.5%	0.86	162.5	0.5%	N/A	N/A	N/A	0.86*	162.5*	0.5%

All parameter distributions Beta(a,b)

- Continuity correction for intervals with no events

* - Assumed as family history detection

3.5.2 Long-term survival

A topic review of evidence on long term survival in SCID was undertaken identifying four studies with potentially relevant evidence.(3, 20-22) The study by Eissa et al (20) reported long term survival for those SCID patients who survived to 2 years post-transplant where overall survival was 90%. The most common causes of death were chronic infections (37.5%) and pulmonary causes (22%). However, this survival was not disaggregated between early and late SCID detection.

The study by Thaker et al(21) has the benefit of reporting survival in 3 cohorts with screening differentiated from family history early detection. The 5 year survival for the three groups was: 79.9% for those with clinical presentation, 85.4% with a family history presentation and 92.5% for screen detection. Whilst it may not be statistically significant it is notable that the clinical presentation survival is similar to that demonstrated for symptomatic detection in the UK retrospective study, though the survival in family history detected patients in the UK cohort is more in line with Thakar et al's screen detected cohort. Whilst this is an important analysis it does not provide the long term survival to extend beyond the scope of the existing UK retrospective cohort.

The Lankester et al study (22) reports survival at 2 years disaggregated by early and late transplantation in a European setting. For SCID patients transplanted at <3.5 months survival was 78.8% and for those transplanted later survival was 75.8% with no significant difference between the two groups.

The long-term mortality rates for patients with SCID are modelled using data from the US epidemiological study conducted by Hardin et al.(3) This study was the most recent to include long-term follow up data, comparing outcomes differentiated between an earlier and a later transplant cohort. The study analysed overall survival (OS) estimates for SCID patients who underwent HSCT at Duke University Medical Center between 19 May 1982 and 1 August 2019. Kaplan-Meier OS curves were reported separately for patients transplanted before 3.5 months of age (N=55) and those transplanted after 3.5 months (N=122). In our analysis, we assumed that the former group represented early-diagnosed SCID patients, whereas the latter group corresponded to late-diagnosed SCID patients. As the study authors didn't provide Individual patient data (IPD), we used the application IPDfromKM to reconstruct IPD from these Kaplan-Meier curves, which was then used to conduct survival analysis.(23)

Parametric survival analyses were performed on these data to estimate OS for the early- and late-diagnosed SCID subgroups for use in the Model. The approach adhered to the methodological guidance outlined in the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD 14).(24) Six standard parametric models were fitted to the available IPD, including the exponential, Weibull, Gompertz, lognormal, log-logistic, and generalised gamma distributions. Model fit was evaluated using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), where lower values indicate superior relative goodness-of-fit. Parametric survival models were implemented using the 'streg' package in Stata.

Model selection for the base-case analysis was determined through a combination of statistical goodness-of-fit (AIC/BIC), visual inspection, and consideration of the long-term extrapolation plausibility. AIC and BIC statistics for the early- and late-diagnosed SCID subgroups are presented in Table 6 and Table 7 respectively. Observed Kaplan Meier OS alongside predicted survival curves for both early and late detected subgroups are depicted inFigure 9 and Figure 10 respectively. The lognormal distribution was ultimately chosen as the most appropriate model for inclusion in the economic analysis for both early- and late-diagnosed SCID patients.

The lognormal survival curves for each subgroup are constrained using general population mortality rates derived from life tables for England.(25) The final constrained and weighted lognormal survival models are illustrated in Figure 11.

Table 6 Model fit statistics for early diagnosed SCID

	AIC	BIC	Rank AIC	Rank BIC
Exponential	41.11161	43.11895	5	4
Weibull	38.6777	42.69236	2	2
Gompertz	42.99052	47.00519	6	6
Lognormal	38.64271	42.65738	1	1
Log logistic	38.70627	42.72093	3	3
Generalised gamma	40.64596	46.66796	4	5

Table 7 Model fit statistics for late diagnosed SCID

	AIC	BIC	Rank AIC	Rank BIC
Exponential	420.9531	423.7571	6	6
Weibull	332.5412	338.1492	4	4
Gompertz	374.4035	380.0116	5	5
Lognormal	328.4193	334.0274	2	1
Log logistic	331.2231	336.8311	3	3
Generalised gamma	327.1092	335.5213	1	2

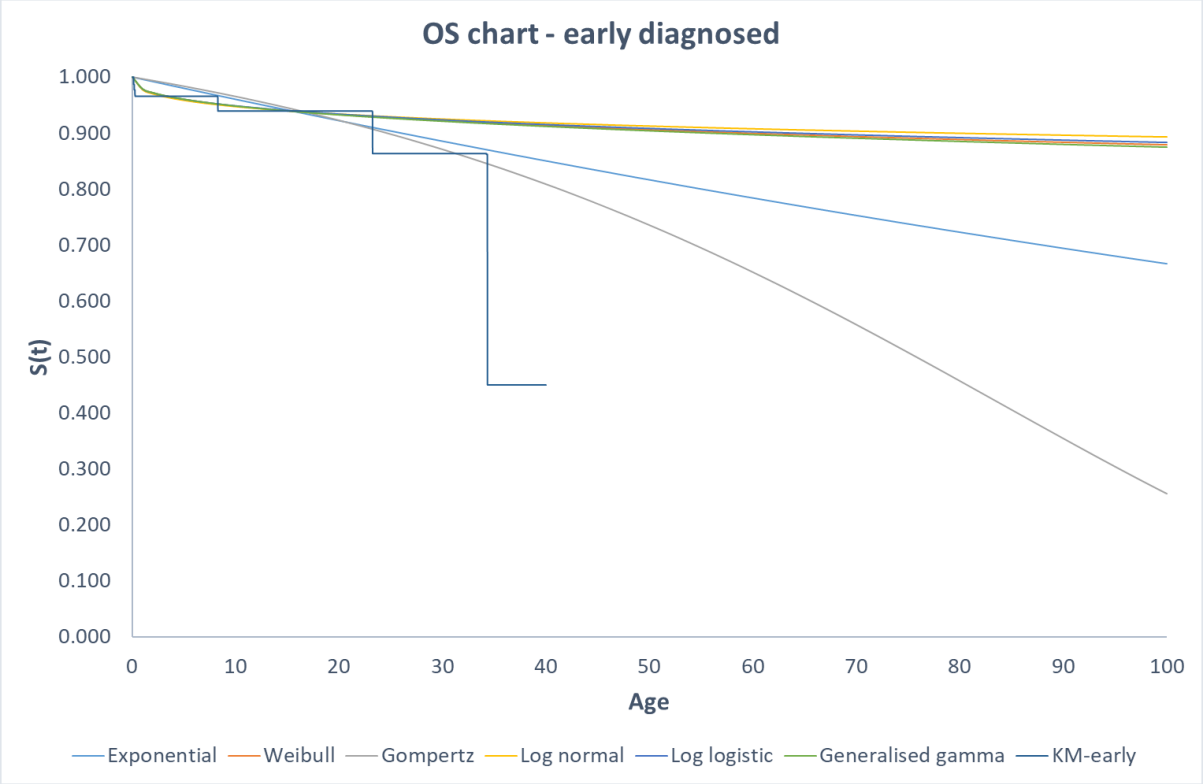


Figure 9 Modelling of overall survival in early detected SCID patients from Hardin et al(3)

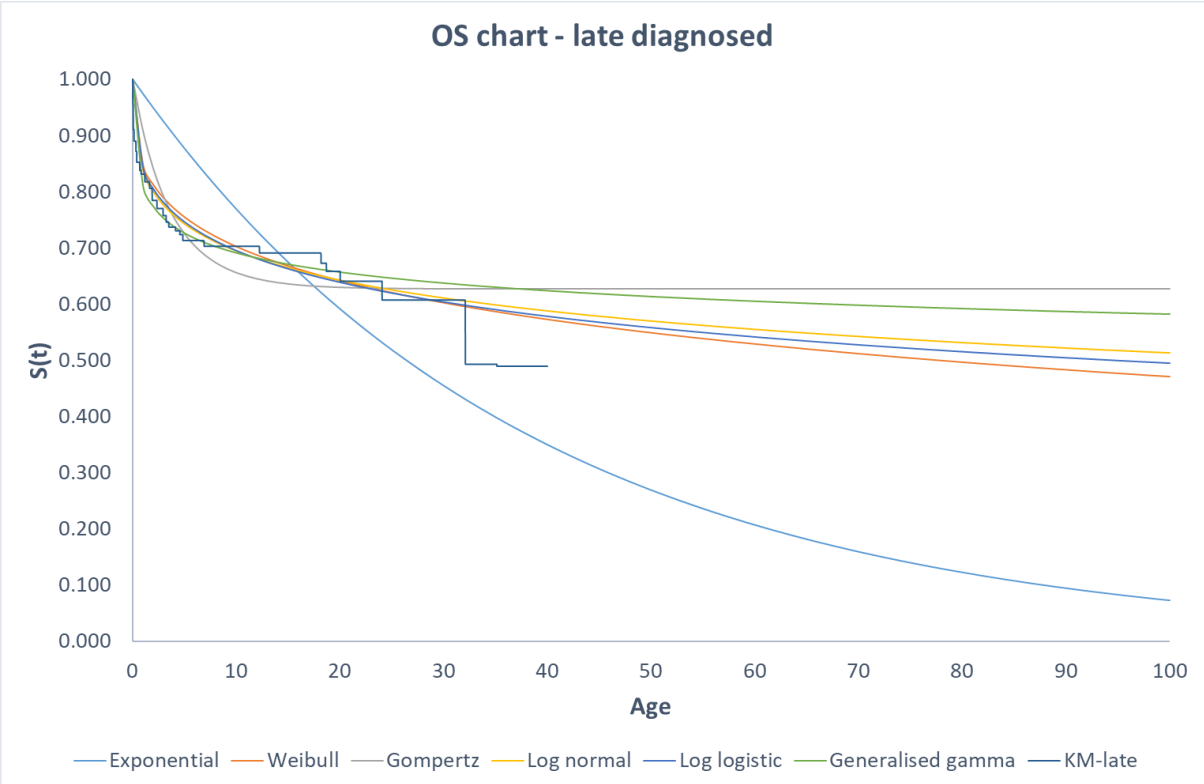


Figure 10 Modelling of overall survival in late detected SCID patients from Hardin et a(3)

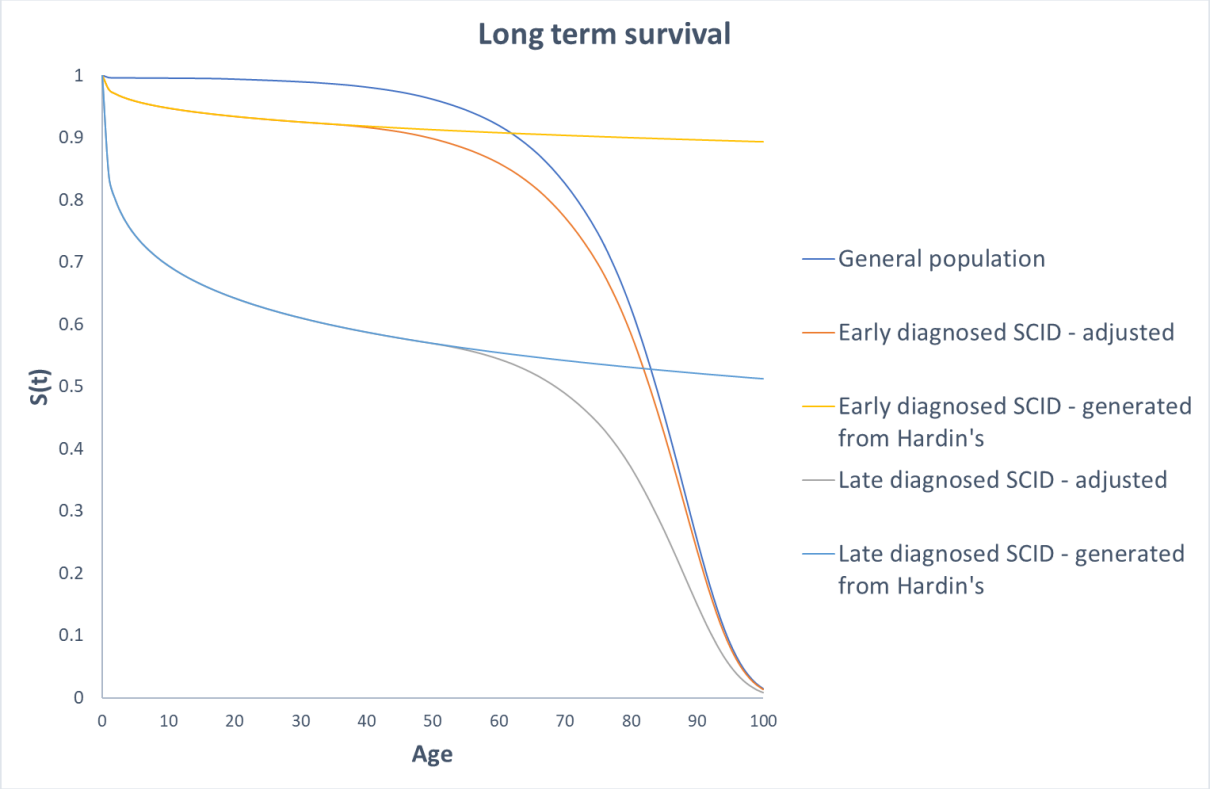


Figure 11 Long-term SCID survival from Hardin et al constrained by ONS England all-cause mortality.

3.5.3 Overall SCID model survival

Overall survival for SCID patients in the Model is combined from 0 to 10 year mortality from SCID treatment in England and long term mortality from the Hardin et al study constrained by all-cause mortality in England. Figure 12 presents the overall survival for SCID groups compared against the full England SCID retrospective data.

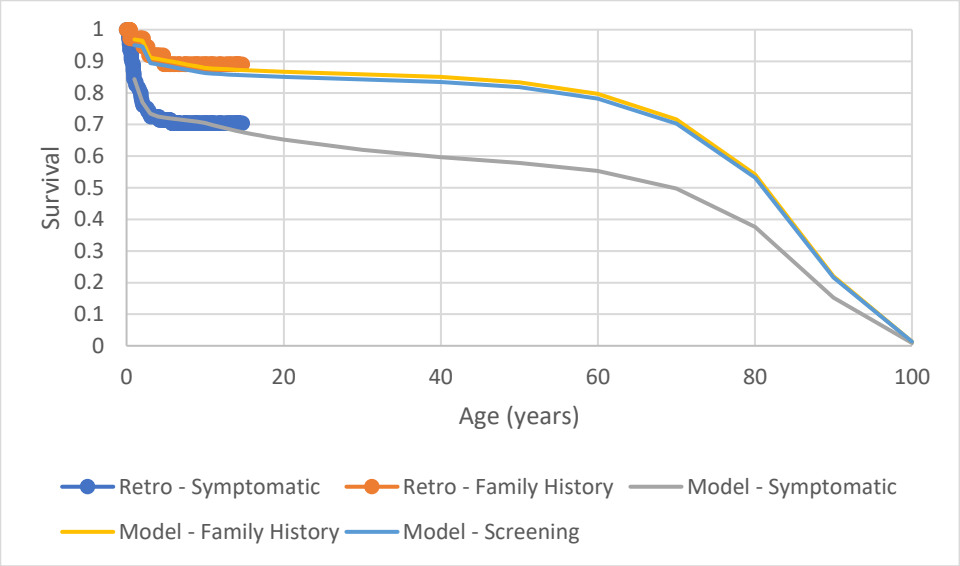


Figure 12 Modelled SCID survival and the England retrospective data

3.6 Treatment outcomes, morbidity and quality of life in SCID patients

3.6.1 Introduction to morbidity and quality of life

Outcomes for SCID patients following successful transplant are generally good, however they are at increased risk of neurological, neurodevelopmental, pulmonary, hepatic, autoimmune conditions and malignancies that have the potential to impact on morbidity (and mortality). Factors that are thought to influence outcomes include SCID genotype, conditioning type, infection status at transplantation and age at transplantation.

The evidence concerning the impact of earlier transplantation, through family history or screen detection, on long term morbidity is inconclusive.(3, 4) Clinical outcomes were similar in the Hamid study in both those diagnosed in the newborn period and those diagnosed later. Higher rates of medical conditions were found in the Hardin et al study in those transplanted ≥3.5 months although the difference was not statistically significant. There is evidence that those who are infected at the time of transplant have a higher rate of chronic and late effects. There is also evidence that the probability of having a chronic/ongoing medical issue increases with age. (20)

The doctoral research published in 2017 at the University of Newcastle by Intan Juliana Abd Hamid investigated the clinical, immunological and psycho-social outcomes in SCID patients who underwent HSCT.(4) This research included evaluation of quality of life using the PedsQL instrument and explored the impacts in different patient groups, including SCID genotypes, in patients diagnosed within and without the newborn period. This dataset comprises the only quality of life data on the outcomes of HSCT in UK SCID patients currently available.

Research, published mainly since 2017, has also investigated the potential to map PedsQL scores to QALY utilities. These mapping algorithms have been used together with the Abd Hamid dataset to generate estimates of QALY utilities following HSCT. The following reports this mapping exercise.

3.6.2 Methods for estimating quality of life in SCID patients

3.6.2.1 The Abd Hamid PedsQL data

The PedsQL instrument comprises 23 item questions in four health related domains. The four domains are physical functioning (PF), emotional functioning (EF), social functioning (SF) and school functioning (FU). Each item is transformed to give a score between 0 and 100, where 100 is good. A PedsQL domain average score (0-100) and total PedsQL average score (0-100) are calculated.

Data was collected from SCID patients who underwent HSCT between 1987 and 2012 at Newcastle. Anonymised patient level PedsQL data is available at the domain level. The potential population included 88 SCID patients. However not all patients and/or parents completed PedsQL questionnaires. Abd Hamid reports that where a PedsQL response was recorded, all items / domains were completed, that is there was no missing data within a PedsQL return.(4)

Abd Hamid collected data on the time of SCID diagnosis and dichotomised this into diagnosis in the newborn period and beyond. HrQoL utilities are analysed according to this categorisation of age of diagnosis.

3.6.2.2 Deriving HrQoL utilities from PedsQL data

Six mapping algorithms(26),(27),(28),(29),(30),(5) and one PedsQL based utility instrument, PedsUtil (31) have been identified through searches and citation tracking. The PedsUtil instrument(31) relies on item level responses and therefore was not feasible to implement in this analysis and is not discussed further. The PedsQL utility mapping papers identified are presented in Table 8.

Table 8 PedsQL utility mapping algorithms

Publication	Population characteristics				Utility instrument
	Country	Population description	Age range	n	
Khan et al (2014)	England	Cross sectional survey of secondary school children	11-15 years	559	EQ-5D-Y (York A1)
Lambe et al (2018)	UK	RCT of prednisolone therapy for treatment of childhood corticosteroid sensitive nephrotic syndrome.	5 - 13 years	563	CHU-9D
Mpundu-Kaambwa et al (2019)	Australia	Community based sample	15-17 years	755	CHU-9D
Sweeney et al (2020)	Australia	Longitudinal Study of Australian Children	10-12 years	1801	CHU-9D
Shafie et al (2021)	Malaysia	Transfusion-dependent thalassemia patients	3-18 years	345	EQ-5D-3L
Kelly et al (2023)	England	Children and Young People's Health Partnership (CYPHP). Ethnically diverse and deprived area of South London, including children with chronic conditions (asthma, eczema or constipation).	0-16 years	1198	CHU-9D

Issues arising from a comparison between studies are:

- Kelly preferred over Lambe and Khan due to fuller age, health and IMD coverage in the mapping population & bigger population.
- Sweeney preferred over Mpundu-Kaambwa since the latter uses the PedsQL 15 item short form rather than the full 23 item version.
- The preferred mapping from Sweeney includes age, despite the restricted age range represented in the population – suggesting potential problems in generalisation.
- Kelly preferred to Sweeney, due to UK population and greater generalisability.
- Kelly preferred to Shafie due to the population relevance.
- All studies apart from Kelly, identify inadequate representation of lower health states in mapping populations – implying potential limits to generalisability.

Based upon the population characteristics summarised in Table 8 and the above notes, the mapping by Kelly (5) is the preferred option for providing utilities for the economic analysis of screening for SCID within the NHS. The mappings by Sweeney and Khan would potentially be bases for additional sensitivity analyses.

The algorithm for mapping from PedsQL dimension scores to CHU9D utilities recommended by the Kelly paper(5) is defined below.

$$CHU9D = \alpha + \beta_{PF}.PedsQL_{PF} + \beta_{EF}.PedsQL_{EF} + \beta_{SF}.PedsQL_{SF} + \beta_{FU}.PedsQL_{FU} +$$
$$+ \beta_{PF2}.PedsQL_{PF}^2 + \beta_{EF2}.PedsQL_{EF}^2 + \beta_{SF2}.PedsQL_{SF}^2 + \gamma_{age}.Age$$

Where the coefficients are, (sd presented in paper):

α = 0.58625

β_{PF} = -0.0015

β_{EF} = 0.0057

β_{SF} = 0.00012

β_{FU} = 0.00106

β_{PF2} = 0.00002

β_{EF2} = -0.00002

β_{SF2} = -0.00000467

γ_{age} = -0.00232

Note, that to avoid potential problems with extrapolating the age factor beyond 18 years, 'Age' is truncated at 18 years.

3.6.3 Results of quality of life modelling for SCID patients

3.6.3.1 Age and the use of parental proxy assessments.

Table 9 gives the distribution of patient and parental PedsQL returns with response data available for mapping by age group. For example, in the <6 years age group, there was insufficient PedsQL data for applying the Kelly mapping for 10 out of 19 patients, for 3 there was both patient and parent data, 6 had only parent data and there were 0 patients for whom there was only patient data. Note that 3 patients who were 2 years old had parental PedsQL data but with no school functioning assessment, these patients were excluded from the analysis. Including parent proxy data increases the available sample from 3 to 9 patients.

Table 9 Patient and parental PedsQL data returns by age group

Age Group		Parent completed		Grand Total	Any PedsQL completed
		FALSE	TRUE		
<6 years old		10	9	19	9
Patient completed	FALSE	10	6	16	
	TRUE	0	3	3	
6-12 years old		10	15	25	18
Patient completed	FALSE	7	3	10	
	TRUE	3	12	15	
13-17 years old		11	17	28	19
Patient completed	FALSE	9	1	10	
	TRUE	2	16	18	
>18 years old		12	4	16	10
Patient completed	FALSE	6	1	7	
	TRUE	6	3	9	
Grand Total		43	45	88	56
Patient completed	FALSE	32	11	43	
	TRUE	11	34	45	

As highlighted in the Kelly paper, children of a certain age or condition may require an adult or guardian to complete the questions, with the consequent potential for introducing proxy biases. For this analysis we primarily use patient scores where available and only otherwise parental scores. That is, where both a patient and parental score is available the patient score takes precedence. Thus, there are 45 patients with a patient completed PedsQL score, 45 with a parent completed score and 56 patients with any PedsQL score available.

Clinical advice was sought from the treating centre for one patient for whom there was a greater than 80 point difference between patient and parental assessed total PedsQL scores (92.4 versus 3.26). Clinical advice was that in this case the parental score should take preference.

There may be concerns about the relevance and validity of PedsQL scores in patients over 18, for example especially in school functioning responses where there was a score of 0 in school functioning in 2 of 10 patients. Analysis of CHU9D valuations for patients < and >18 years of age is therefore presented in Table 10, which suggests there may be an issue with utility assessment for the >18 years age group.

Table 10 CHU9D utilities by age group

	CHU9D (Patient/Parent)		
Age Group	n	Mean	Sd
<6 years old	9	0.926	0.113
6-12 years old	18	0.917	0.091
13-17 years old	19	0.929	0.095
>18 years old	10	0.873	0.141
Grand Total	56	0.915	0.105

3.6.3.2 Utility for early and late detected SCID patients

Table 11 presents the mean CHU9D utility scores for SCID patients by the SCID genotype groups presented in Abd Hamid's thesis, together with the difference in utilities between newborn and late diagnosed patients in these groups. The clinical justification for these groups is provided in Abd Hamid's thesis. The results show that the mean utility gain for SCID patients diagnosed in the newborn period over later diagnosed cases in all genotype groups are consistently in the range +0.064 to 0.089.

Table 11 CHU9D utility differences between SCID patients diagnosed in the newborn period and later by SCID type.

CHU9D (Patient/Parent)	Late diagnosed			Newborn diagnosed			Total			Newborn - Late	
Genotype group	n	Mean	StdDev	n	Mean	StdDev	n	Mean	StdDev	Mean	StDev[a]
ADA SCID	9	0.891	0.109	2	0.954	0.046	12[b]	0.910	0.100	0.064	0.118
Artemis & RAG 1/2	5	0.887	0.091	5	0.955	0.046	10	0.921	0.077	0.068	0.102
IL2RG/JAK3 SCID	12	0.891	0.131	6	0.981	0.029	18	0.921	0.115	0.089	0.134
IL7Ra SCID	7	0.865	0.153	4	0.937	0.112	11	0.891	0.138	0.072	0.190
Others & Undefined SCID	5	0.945	0.060	0	N/A	N/A	5	0.945	0.060	N/A	N/A
Grand Total	38	0.893	0.115	17	0.960	0.060	56	0.915	0.105	0.067	0.130

a - StDev estimated assuming newborn and late diagnosed independent

b - 1 ADA patient with unknown time of diagnosis

It is assumed that the SCID patients diagnosed in the newborn period are a reasonable proxy for screen diagnosed SCID patients. It is further assumed that the mean HrQoL utility for the two SCID patient groups has a Beta distribution.

The parameters of the Beta distribution, a and b, are estimated from the mean and variance where:

The mean of a beta distribution is: a/(a+b)

The variance is: (a*b)/(a+b)^2*(a+b+1)

Therefore, the HrQoL utility distributions for late symptomatic detected SCID patients is u_{late} and screen & family history detected (newborn detected) patients is $u_{newborn}$ where:

u_{late} ~ B(244.1, 29.4)

u_2 ~ B(176.8, 7.5)

$u_{newborn} = \max(u_{late}, u_2)$

If it is assumed that the mean utility in early detected SCID patients must be greater than or equal to late detected patients.

3.7 Parental quality of life utility impacts of SCID screening results

3.7.1 Methods for estimating parental quality of life impacts of SCID screening results.

A research study undertaken in parallel with the NHS Evaluation of screening for SCID explored the impact of screening on parents and health professionals.(2) The study explored the impact of screening on parents who received a positive screening test result suggesting T-cell lymphopenia (TCL). This included babies with a normal result on flow cytometry (false positive), babies who went on to have a confirmed diagnosis of SCID and babies whose screening result suggested they may have another disorder affecting their immune system (non-SCID TCL). The study used mixed methods to collect qualitative narrative descriptions of people's experiences together with quantitative HrQoL instrument data.

The quantitative data collected in the research study comprised EuroQol 5 Dimension score (EQ5D) and visual analogue scale (EQ5D-VAS), the Generalised Anxiety Disorder questionnaire (GAD-7) and the Infant Toddler Quality of Life Questionnaire (IT-QOL). The protocol specifies quantitative data collection at six time points, at 12 month intervals up to 5 years. Due to practical issues in recruitment and follow up, responses are allocated to the closest time point. The full research report(2) presents analyses of data collected at the first three time points 0-12 months (T1), 12-24 months (T2) and 24 months (T3).

Key narrative results taken from the Executive Summary of the research report(2) are:

- Positive screening results from SCID screening are distressing for parents. This is particularly true for parents whose baby is an inpatient and is already grappling with the additional stresses associated with having a sick newborn.

- True positive SCID, non-SCID TCL and false positive screening results, can lead to parental concerns about their child's vulnerability and can lead to parents isolating their children to prevent them being exposed to infections. Parents also reported altering life plans in response to their child's screening result which included decision making concerned with returning to work, enrolling their children in nursery and future reproductive plans.
- However, for children with a false positive screening result for SCID, these concerns had mostly resolved by the time the child reached their first birthday as they started to be exposed to common childhood infections and their parents could see evidence of them mounting an appropriate immune response. Positive screening results for SCID had the potential to positively impact parenting relationships but could negatively impact parental mental health; the latter did not appear to resolve over time.

The full quantitative results of the parallel research study are presented in the original report(2) in Tables 3-6.

The maximum numbers of patients completing EQ5D questionnaires in the different patient categories are: 20 false positives (T1), 3 SCID (T2), 4 Non-SCID TCL (T1) and 2 negative results (T1).

3.7.2 HrQoL utility impacts for parents of a SCID diagnosis

For parents of patients who receive a confirmed diagnosis of SCID the appropriate comparison is between SCID diagnosed through screening and SCID diagnosed otherwise. The small number of returns in the SCID category means that the estimates of parental utility are subject to a high degree of uncertainty. There is, therefore, insufficient data to measure the comparative impacts directly. Whilst dealing with a diagnosis of SCID undoubtedly has major impacts on parents, it is assumed in the economic modelling that the mode of diagnosis has no impact. Where SCID results in infant death the incorporation of the impact of parental bereavement are described below.

3.7.3 HrQoL utility impacts for parents of babies who receive a false positive result.

Table 12 presents the EQ5D results for the parents of babies who receive a false positive result compared to the described population norms, drawn from Table 3 of the research report.(2)

Table 12 EQ5D scores for parents of babies receiving a false positive result

Time point following birth		T1 0-12 months	T2 12 months	T3 24 months
Parents of a baby with a false positive result	Mean EQ5D SD N SE	0.82 -0.2 20 -0.045	0.85 -0.18 12 -0.052	0.98 0 4 N/A
Population norm*	Mean EQ5D SD n SE	0.86 -0.18 493 -0.008	0.93 -0.15 423 -0.007	0.93 -0.15 423 -0.007
EQ5D Difference (norm minus observed)		-0.04	-0.08	0.05
SE Difference		0.045	0.052	N/A

* T1 value for a UK postnatal population,(32) T2 and T3 values from UK general population norms (33) (Table A) relating to for females aged 25-34.

The qualitative results from parental interviews undertaken as part of the research are clear in identifying that false positive results have a negative impact on parents and impact on parental behaviours. These qualitative results are supported by the ITQOL analyses, that identify good evidence of reduced health related quality of life within the first year for both the parent and child. Further, there is strong evidence from ITQOL of reduced general health perceptions in the false positive group at one year post birth, together with strong impact of lower parental emotional impact scores.

The EQ5D results in Table 12 are consistent with the qualitative and ITQOL analyses in identifying a potential small effect in the first year post birth.

The difference in HrQoL utility for parents receiving a false positive result compared to a negative screening result, u_{FP} , is therefore estimated to be a truncated Normal distributed for the economic modelling:

$$u_{FP} \sim \min(0, N(-0.04, 0.045))$$

The truncation is implemented on the assumption that a false positive result is unlikely to lead to HrQoL gain. The truncation will mean that in approximately 20% of probabilistic sensitivity analysis (PSA) samples a false positive result will be associated with no quality of life detriment. Whilst this truncation will also lead to an increase in the mean disutility this will not be out of line with the disutility estimated at the T2 sample point.

3.7.4 HrQoL impacts in babies with Non-SCID TCL

The small number of returns in the Non-SCID TCL categories, similarly means that estimates are subject to high levels of uncertainty. The relevant comparison for parents & patients who receive a Non-SCID TCL screening result depends on the individuals counterfactual without screening. For many patients that have an underlying immunological condition or health condition with an immunological component, the impact of mode of diagnosis may be minimal. Where diagnostic investigation following a positive SCID screening result is inconclusive or labelled as idiopathic TCL, the impacts on parents, especially where a baby is otherwise asymptomatic, may be negative. Furthermore, where the TCL does not resolve direct parental impacts may be long lasting. Unfortunately, whilst there is strong evidence from ITQOL of reduced general health perceptions in the Non-SCID TCL group at one year post birth, it has not been possible to measure the appropriate marginal impacts in utility directly within the parallel research. These effects are explored further in a narrative discussion in the research study report.(2) The economic modelling enumerates the numbers of patients/parents who fall into the different categories of benefit and utility disbenefits are assigned for each category as presented in Appendix 3: Model categories for Screen positive cases.

3.8 Parental quality of life utility impacts of bereavement

A topic search for health economic studies that address the HrQoL utility impact of parental bereavement identified a set of studies undertaken to inform either NICE or JCVI policy questions (34-36) that all trace back to original research published by Song et al in 2010 on the long term effects of child death on parental quality of life in Wisconsin in the US.(37) This was the best evidence available until the landmark publication in 2024 of a study from Manchester in the UK by Camacho et al.(6)

The Camacho authors undertook an online survey of mothers and fathers in the UK who had experienced perinatal death. The survey included assessment of HrQoL using the EQ-5D-5L instrument, using the English value set recommended by NICE at the time of the study, and compared responses with matched general population values to estimate the impact of perinatal death. The study analysed responses by time since perinatal loss to estimate how quality of life impact changes over time. The Camacho et al study (6) is used in the Model as the basis for estimation of a quality of life decrement associated with bereavement for a mother / father (birth parent / birth partner) dyad.

The absolute cumulative utility shortfalls up to 10 years for mothers (Table 4 of the paper) are used together with the relative father/partner estimates (Table 2 of the paper) to estimate annual utility shortfalls. These annual shortfalls are used to estimate discounted cumulative parental bereavement utility losses. The whole sample values calculated in this way are validated against reported estimates.

The model assumes that utility shortfalls are Normally distributed with the mean and standard errors presented in Table 13. The bereavement impacts are implemented for SCID deaths up to age 18 years.

Table 13 10 year cumulative utility impact of perinatal bereavement

Discount rate	QALY decrement (discounted)	Mean	SE	Lower 95%CI	Upper 95%CI
Undiscounted	Mothers only	-1.12	0.11	-1.33	-0.90
	Fathers	-0.52	0.26	-1.03	0.00
	Parent dyad	-1.63	0.13	-1.88	-1.38
Baseline 3.5%	Mothers only	-0.94	0.09	-1.12	-0.76
	Fathers	-0.44	0.22	-0.87	0.00
	Parent dyad	-1.38	0.11	-1.59	-1.17
1.5%	Parent dyad	-1.51	0.12	-1.74	-1.29
5%	Parent dyad	-1.29	0.10	-1.48	-1.09

3.9 Costs of screening

3.9.1 Laboratory costs of screening

The cost of implementing screening with the IIVD real time PCR screening test is estimated based upon experience in the SCID Screening Evaluation. The laboratory cost of screening is broken down into staff costs, test costs, IIVD equipment, other laboratory items, large equipment costs and estate costs. Each category is described in more detail.

Staff costs

Staff costs are based on the costs allocated to the participating laboratories in the SCID Screening Evaluation including on-costs and hosting costs. The Evaluation laboratories, excluding GOSH, received funding for 1 x band 7 and 0.2 band 8a staff. GOSH received higher funding, including 2 x band 5 and 0.5 band 7. GOSH has been excluded from the staff cost calculations for the model, as going forward they are expected to have an increased staff cost. To estimate an overall UK cost, it is assumed that the laboratories not actively included in the Evaluation would have a staff cost equivalent to the non-GOSH Evaluation laboratories. Given that the non-evaluation laboratories on average screen less babies per year than the Evaluation laboratories, the expected staff cost for a UK wide roll out is higher at £3.50 per baby screened compared to the Evaluation cost at £2.53 per baby screened. The calculation of staff costs is presented in Table 14.

IIVD Costs per baby tested

The costs per baby tested for IIVD are shown in Table 15. This takes into account the average number of patient samples per plate, assuming 17 non -patient standards, QCs and blanks per plate, the overall repeat rate and duplicate rate and the number of plate failures to give a cost per baby screened. Note that the repeat and duplication rate is estimated from the Evaluation and is screening algorithm dependent. The model provides the facility to evaluate the three screening algorithms for which results are analysed as previously discussed, though the cost difference is minimal. We have assumed a 2% plate failure rate (average of GOSH and NUTH) which as shown in Table 15 adds an extra £5 to the cost of each plate run. In addition to this each laboratory will also need to run an average of 5 plates per year for QA purposes which is shown in Table 16.

IIVD equipment

All laboratories require at least 2 RT TCPs and Thermal cyclers. We have assumed a 6 year lifespan for the equipment with 10% per year for maintenance costs and have based the cost per baby screened on three evaluation laboratories.

Other laboratory items

The other category includes the cost of small equipment such as centrifuges, flow cabinets, laboratory fridge and freezer. Along with the other equipment we have assumed a 6 year lifespan and 10% per year for maintenance costs. This makes up the higher proportion of the other category at 14p per baby screened. Consumables made up 3p per baby screened and the one-off costs of the extra UKAS visit per lab and lab software modification of 2p per baby screened over a 10 year period.

Large equipment costs

Large equipment costs included ensuring laboratories had sufficient back up equipment such as Panthera or DBS puncher. Based on the evaluation where 2/7 laboratories required additional back up equipment, we have assumed that UK wide 28% of laboratories would require this equipment. For this equipment we have assumed a 6 year lifespan with 10% per year for maintenance costs.

Estate costs

To include the necessary equipment for SCID screening some laboratories required estate changes. These differed between the evaluation laboratories. Assuming a 10 year lifespan the costs per baby screened was low. Estate costs for non-evaluation laboratories may be higher as one of the criteria for selection for evaluation laboratories was the ease of implementing SCID screening. However, as the cost per baby screened is very low it is assumed that this would not have an impact on the overall costs.

Table 14 Screening laboratory staffing costs (all tests)

Lab	Staff costs*	Babies screened (2021/22)	Staff cost per sample
Manchester	£134,000.00	53000	£2.53
Sheffield	£134,000.00	65000	£2.06
Birmingham	£134,000.00	67000	£2.00
Newcastle	£134,000.00	30000	£4.47
SET	£134,000.00	53000	£2.53
SWT	£134,000.00	50000	£2.68
Total (Evaluation)	£804,000.00	318000	**£2.53**
Additional 9 laboratories at 134,000 per annum	£1,206,000.00		
Total 16 laboratories (UK excluding GOSH)	£2,010,000.00	574257	**£3.50**

*allocation was for 1wte Band 7 and 0.2wte Band 8a + 20% on-costs + hosting costs (approx. £134,000 per annum including on-costs)

Table 15 Cost per baby screened IIVD

	Cost per sample (€)	Minus VAT (20%)	Conversion to £	Samples per plate	Cost per plate (£)	Cost plate failure (2%)	Cost per plate inc plate failure (£)	Patient samples per plate	Cost per patient sample (€)	Combined Repeat & duplicate rate	Cost per baby screened
Total	3.50	2.92	2.51	96.00	240.77	4.82	245.59	79.00	3.11	0.28%	3.12

Table 16 IIVD QA costs per laboratory

QA plates per year	Cost per plate (£)	Total cost per year	Number of laboratories	Total cost	Number of births	Costs per baby screened
5	240.772	1203.86	16	19261.76	689257	0.028

Table 17 presents the total cost per baby screened comprised from the individual cost categories.

Table 17 Cost per baby screened

Cost category	£
Staff costs	£3.50
Test cost	£3.15
IIVD equipment	£0.63
Other	£0.22
Large equipment costs	£0.06
Estate costs	£0.02
Total	**£7.58**

3.9.2 Potential impact of screening for SCID and SMA on laboratory costs

Independently of the NHS SCID Evaluation, the UK NSC is, in 2025, considering whether to include screening for SMA within the NHS Newborn Bloodspot Screening Programme and the economics of screening for SMA are considered in a separate report.(38)

The economics of screening for SCID and SMA are necessarily intertwined since the introduction of screening technologies that are explicitly designed with the functionality to detect both conditions together. That is, neither of the SCID test kit suppliers considered in the SCID Evaluation, IIVD or Revvity offer a 'SMA only' option of their technology.

It is therefore useful to consider ways of apportioning the costs of screening between the two conditions. The first approach considered is to understand the minimum marginal cost of screening for SCID if one were already screening for SMA (or indeed vice versa). As described above, the laboratory equipment would already be in place and the two assays are performed on the same run so would require little additional analyst time. The required reagents for detecting both conditions are already in the box from both suppliers and hence incur no additional cost.

As a result, the increase in cost would predominantly be the increased staff time for reporting and maintaining both assays, rather than testing both. The marginal cost of considering each condition is therefore related to the relative referral rate. Therefore, in the case of SCID, if the screening algorithm is defined to support a referral rate of approximately 1:5,000 (equivalent to the baseline algorithm A3, see Table 3) then dealing with cases needing repeat or referral would be rare, maybe one or two per month in a lab with a workload of 50,000 samples per annum.

Taken together general housekeeping of results, it is predicted that 0.5 wte Band 7 would be sufficient to cover the workload. At a grade mid-point with employer on-costs this would add approximately 30k per annum, to give an estimate of approximately £0.60 per sample in a workload of 50,000 samples per year to run SCID + SMA compared to SMA alone.

This minimum marginal cost of screening for SCID therefore comprises just under 10% of the total £7.58 per sample laboratory cost of screening described above. This minimum marginal cost of screening for SCID is explored in sensitivity analyses.

An alternative approach to apportioning the costs of screening between the conditions is by the relative birth prevalence. This is equivalent to assuming a constant cost of detection per case for the two conditions. In this case, the birth prevalence of SMA is 1:8200 compared to 1:53000 for SCID. On this basis approximately 14% of the total cost of the screening test would be apportioned to SCID.

3.9.3 Screening confirmation and diagnosis costs

The cost of follow up and confirmation for screen positive cases is based on interviews with three of the immunology services taking part in the Evaluation. Diagrams outlining the confirmation processes were defined with input from the SCID Oversight Immunology Subgroup, the diagrams are presented in Appendix 4. The costs in the model are based on the outpatient costs for three outpatient appointments; 1st for the clinician to contact the parents and arrange the appointment, 2nd for initial appointment where blood is taken and the process explained, and 3rd for the result to be given to the parents/carers. This cost is applied to all screen positive cases, except those who die and who are identified with an inconclusive final designation. The cost of immediate follow up for screen positive cases is estimated at £1034 per case.

In the screened arm, babies who are not identified as false positive receive further diagnostic investigation and incur related diagnostic costs. The further investigation costs included in the model are described in Table 18. All consultations are assumed to be consultant led clinical immunology and allergy service (Service code 255) outpatient appointment. Genetic test costs are obtained from UK Genetic Testing Network costs published for the year 2015/16 and uprated to 2021/22 costs. The cost for 'sequencing of the entire coding region of gene (s) [SCID, autosomal recessive, T cell-negative, (B cell-negative, Nk Cell-Positive & B cell-positive, Nk Cell-negative)] is used as the cost for diagnostic investigation for SCID and the full genetics is the primary immune deficiency syndromes 206 exome panel. For patients who are identified with syndromic and non-syndromic TCL it is assumed that symptomatic diagnosis would occur at some and that therefore there are no marginal diagnostic test costs. For patients who are identified with idiopathic TCL or patients who remained alive at the end of the Evaluation but were identified as inconclusive non-SCID TCL, the model includes additional costs for 1x flow cytometry, 3x immunology appointments and 1x full genetics panel.

Without screening, the costs of SCID diagnosis for both symptomatic and family history detected patients are assumed to be the same as under screen detection. Note that diagnostic odyssey costs for symptomatically diagnosed SICD patients are included in the management costs below.

Table 18 Diagnostic costs for non-SCID TCL additional to initial flow cytometry

Final classification	Diagnostic resources included in model	Cost
SCID diagnosis	1*immunology service app. + 1*SCID genetic test	£952
Syndromes with non-SCID TCL	Assumed no marginal cost	£0
TCL secondary to other conditions	Assumed no marginal cost	£0

Reversible TCL - potential disbenefit	1x flow cytometry, 2x imm app.	£722
Idiopathic non-SCID TCL	1x flow cytometry, 3x imm app., 1x full genetics panel	£2,500
Inconclusive TCL, alive at last follow up	1x flow cytometry, 3x imm app., 1x full genetics panel	£2,500
Inconclusive TCL, patient died.	Assumed no marginal cost	£0

3.9.4 SCID Management

The secondary care costs of managing patients identified with SCID is principally estimated from the HES activity identified for the retrospective cohort of SCID patients identified by NUTH and GOSH and the SCID patients identified by screening within the SCID Evaluation. The analysis differentiates SCID patients by mode of detection, that is symptomatically, family history or screen detected. This presentation route for individuals was provided by NUTH and GOSH for the retrospective SCID cohort and by the Evaluation for screen detected and linked to the HES data. The HES activity includes admitted patient care (APC), outpatient (OP) and emergency department (AE and ECDS) activity. All HES activity for each identified SCID patient is included in the analysis, specifically this includes all activity prior to and post SCID detection. It should be noted that this means that the diagnostic odyssey of symptomatically diagnosed patients is included in the analysis. Due to time constraints the diagnostic odyssey costs have not been separately analysed and presented.

The identification of definitive treatment activity, that is HSCT, GT and TT, is inconsistent within HES compared to the retrospective activity data provided directly by GOSH and NUTH. Therefore, definitive treatments for SCID are costed separately as described below.

Annual SCID management costs are calculated for all SCID patients for all full years of follow up. That is final part years are excluded from the analysis. To account for potentially higher costs associated with end of life, costs in the last 6 months of life for patients who die are calculated separately as described below. Costs are generated for APC spells including calculation of critical care day costs, OP and emergency episodes.

The annual cost of secondary care management for SCID patients who survive to the start of the year, excluding definitive treatment (HSCT etc) costs and mortality costs is presented in Figure 13. Annual management costs for SCID patients reduce consistently for the first 7 years after birth. Costs for symptomatically detected patients are consistently higher than family history or screen detected patients for this period and thereafter annual costs settle down and are not significantly different for family history or symptomatically detected patients. Costs in screen detected patients are only available for up to 2 years follow up, with n=11 in year 1 and only n=4 for year 2. The average annual costs for screen detected patients is similar and not significantly different from family history detected patients in years 1 and 2. Patient level costs are left bounded by £0 and right skewed.

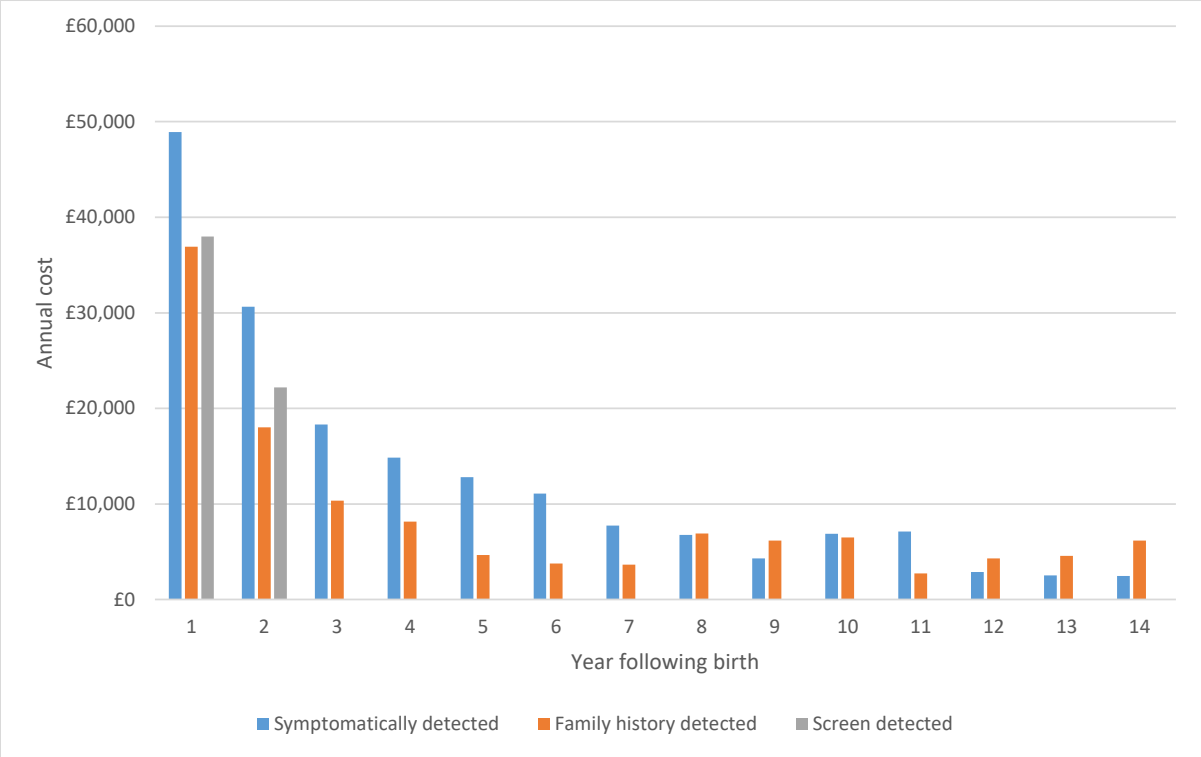


Figure 13 Average annual cost of managing a SCID patient alive at the start of the year excluding definitive treatment and mortality costs

The baseline analysis in the model uses average annual costs by mode of detection up until year 7 and thereafter applies a common annual cost. For screen detected patients, the 1st year costs are derived from the SCID Evaluation, subsequent years are assumed to incur the same costs as family history detected patients. Patient costs in the model are assumed to follow a lognormal distribution with mean and standard deviation calculated from the HES data. Annual costs of SCID management in the model are included in Table 19.

Table 19 Annual full year secondary care costs for SCID patients surviving to the start of the year excluding definitive treatment and mortality costs.

Year		1	2	3	4	5	6	7+
N	Symptomatic	90	88	79	75	69	62	262
	Family History	36	36	34	31	32	28	
	Screening	9	4	0	0	0	0	
Mean cost	Symptomatic	£48,901	£30,630	£18,320	£14,843	£12,815	£11,099	£6,245
	Family History	£36,907	£18,008	£10,342	£8,164	£4,674	£3,766	
	Screening	£37,988	£22,193	n/a	n/a	n/a	n/a	
	Symptomatic	9.916	9.761	9.121	8.582	8.308	8.051	7.717

Mean Ln(Cost)	Family History	9.956	9.001	8.209	7.885	7.423	7.469	
	Screening	10.387	9.081	n/a	n/a	n/a	n/a	
StDev Ln(Cost)	Symptomatic	1.337	1.231	1.377	1.535	1.475	1.591	1.308
	Family History	1.157	1.444	1.523	1.400	1.342	1.223	
	Screening	0.599	1.920	n/a	n/a	n/a	n/a	

Note all annual SICD management cost parameters are lognormally distributed.

For SCID patients within the retrospective cohort who died, the average total cost of management in the 6 months prior to death was £30,847 (sd £44,845). The model assumes a lognormal distribution, mean 9.364, sd 1.592.

3.9.5 Costs of definitive treatment for SCID

Definitive treatment for SCID is identified as HSCT, GT and TT. Clinicians from GOSH and NUTH were asked to identify HRGs that would be associated with definitive treatment. Table 20 presents the HRG codes identified as being potentially associated with definitive treatment, together with the number of spells and spell durations identified within the HES retrospective data, broken down by family history and symptomatic presentation routes.

It can be seen from Table 20 that the average duration of DT spells for SCID patients presenting through family history is approximately 61 days compared to 82 days for those presenting symptomatically. This corroborates clinician feedback that management and treatment of early detected SCID patients is more straightforward and with few complications and will therefore incur a reduced cost compared to late detected SCID patients.

HRG costs are taken from 2021/22 NHS Reference Costs(39) and the weighted average HRG cost is calculated for the overall retrospective data. However, HRG costs do not differentiate between presentation route, the SCID model, therefore, accounts for the lower costs following early detection compared to late detection by adjusting for the different lengths of stay. Two methods of adjustment are considered.

A simple adjustment method is considered, assuming a constant cost per day. This simple method is potentially subject to two biases, firstly the high cost of the transplant procedure itself means the constant cost per day assumption would be likely to overestimate the difference between symptomatic and family history detection. Secondly, if symptomatic patients are sicker than family history detected patients then the simple adjustment would likely underestimate the difference. In order to corroborate costs, a second method based upon the excess bed day costs identified in the Reference Cost method as implemented during the retrospective period is considered. Table 20 presents the derived average DT costs for family history and symptomatically detected SCID patients under the two adjustment methods.

During the SCID Evaluation the average DT spell duration was virtually identical to the family history group in the retrospective cohort at 62 days, though with a sample size of 9. The SCID Model therefore assumes that DT treatment costs following screen detection are the same as for family

history detected patients. The baseline analysis uses the first simpler adjustment method that is the most favourable to screening of the two methods considered, under this method the average cost of DT spell following early family history or screen detection is £77,800 compared to £104,300 following late symptomatic detection.

Table 20 Costs of definitive treatment for SCID

HRG Code	HRG Description	Symptomatic		Family History		Retrospective		HRG Cost	Excess bed day cost 2021/22
		Spells	Avg spell duration	Spells	Avg spell duration	Spells	Avg spell duration		
SA19B	Bone Marrow Transplant, Autograft, 18 years and under	3	31.0	1	1.0	4	23.5	£115,737	£677
SA20B	Bone Marrow Transplant, Allogeneic Graft (Sibling), 18 years and under	13	70.4	8	55.3	21	64.6	£72,733	£976
SA21B	Bone Marrow Transplant, Allogeneic Graft (Volunteer Unrelated Donor), 18 years and under	3	128.3			3	128.3	£141,766	£1,364
SA22B	Bone Marrow Transplant, Allogeneic Graft (Cord Blood), 18 years and under	8	87.0	6	96.3	14	91.0	£133,873	£1,012
SA23B	Bone Marrow Transplant, Allogeneic Graft (Haplo-Identical), 18 years and under	5	103.6			5	103.6	£115,737	£1,012
SA26B	Peripheral Blood Stem Cell Transplant, Autologous, 18 years and under	2	115.5			2	115.5	£38,289	£669
SA38B	Peripheral Blood Stem Cell Transplant, Allogeneic (Sibling), 18 years and under	3	89.7	6	53.2	9	65.3	£69,176	£232
SA39B	Peripheral Blood Stem Cell Transplant, Allogeneic (Volunteer Unrelated Donor), 18 years and under	2	41.0			2	41.0	£80,724	£656
SA40Z	Peripheral Blood Stem Cell Transplant, Allogeneic (Donor Type Not Specified)			1	3.0	1	3.0	£49,133	£582
Grand total / Weighted average		39	81.8	22	61.0	61	74.3	£94,726	
HRG spell cost per day						Simple average		£1,275	£850
DT spell cost, average cost per day method (SE)		£104,253	(£4341)	£77,837	(£3241)	£94,726	(£3944)		
DT spell cost, excess bed day method (SE)		£101,077	(£4208)	£83,467	(£3475)	£94,726	(£3944)		

3.9.6 Enzyme replacement therapy in ADA-SCID patients

Enzyme replacement therapy (ERT) with polyethylene glycol-modified adenosine deaminase (PEG-ADA) is available for patients with ADA-SCID and can improve immune function and provide protection against infection. Whilst ADA-SCID patients are only a small subgroup of SCID patients, the cost of PEG-ADA is high and hence their potential impact of these costs on the economics of screening is considered.

The retrospective cohort study from GOSH and NUTH collected evidence on ERT usage. Only 1 out of 27 ADA-SCID patients recorded in the cohort did not receive ERT therapy. It is therefore assumed in the Model that all ADA-SCID patients receive ERT.

The retrospective cohort shows no significant difference between the duration of ERT in the family history and symptomatically detected groups, see Table 21.

There is no list price for PEG-ADA in the UK. The cost per vial is reported as £10,800 per vial (Personal communication by email A Gennery, 06/02/2025, NUTH), with typically one double dose given once a week (one vial a week, rather than 2).

Table 21 Duration of ERT usage in the retrospective cohort

ADA SCID - ERT given	Count of ERT usage	Average of Duration of ERT (months)	StdDev of Duration of ERT
Family History	6	9.3	7.9
Symptomatic	19	6.5	6.1
Total	25	7.2	6.4

The baseline analysis therefore assumes that the cost of ERT is applied to all ADA SCID patients equally.

It should be noted that the standard deviations of ERT duration are large with respect to the means, indicating very skewed data with a few extended durations. Furthermore, the retrospective data demonstrates an association between the age at first definitive treatment (DT) and ERT usage, as shown in Figure 14. If we consider all SCID patients, that is not just ADA-SCID, the age of first DT is lower in the family history and screen detected groups than in the symptomatically group. This would suggest that screening may have the potential to reduce overall average ERT usage and this is explored in a sensitivity analysis, see Table 22.

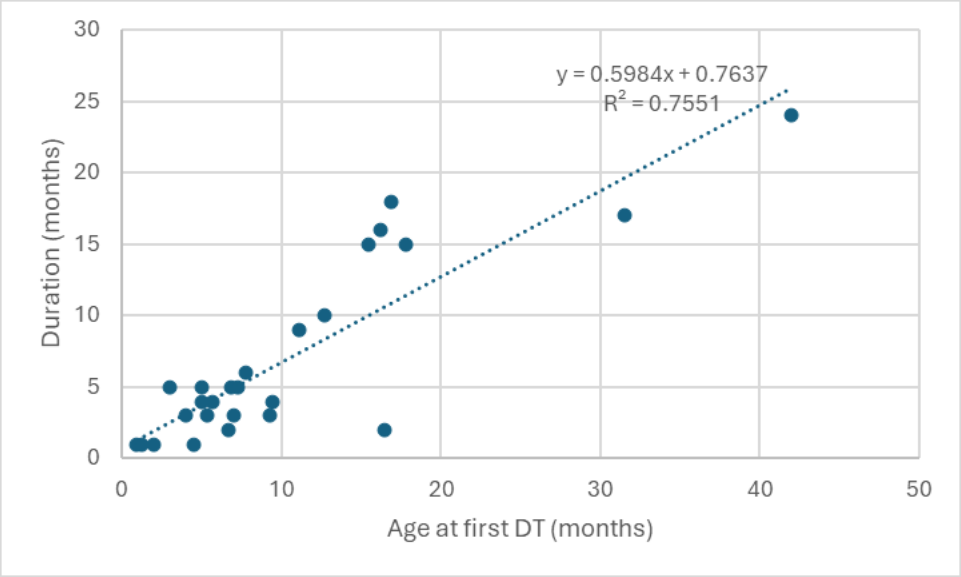


Figure 14 Association between age at first definitive treatment and duration of ERT usage

Table 22 Average age of definitive treatment and implied average duration of ERT usage

Row Labels	Average age of first DT (months)	Age of first DT SE	Average duration of ERT (months)
Family History	2.5	0.5	2.4
Screening	3.9	0.5	3.1
Symptomatic	9.8	1.6	6.6
Grand Total	**6.9**	**8.5**	**6.9**

3.9.7 Immunoglobin replacement therapy

The proportion of patients on immunoglobulin replacement therapy appears to be related to conditioning regime at transplantation rather than timing of diagnosis.(4) The inclusion of costs for intravenous immunoglobulin replacement therapy (IVIG) therefore follows the logic and implementation of IVIG costing in the Highly Specialised Technologies guidance, HST7 Strimvellis for treating ADA-SCID. The logic for the cost estimation is presented in Table 23. These costs are applied to all SCID patients according to survival.

Table 23 Estimation of immunoglobin replacement therapy costs

Cost item	Unit	Comment

IVIG dose (g/kg) every 3 weeks	0.4	After Strimvellis submission - The recommended dosing range is 0.2-0.8 g/kg/month [Gammagard SmPC, 2016]. A 0.4 g/kg dose chosen based on clinical advice The steady state dosing regimen range is 2-4 weeks [Gammagard SmPC, 2016]. The dosing interval was assumed to be the midpoint of the 2-4-week range.
IVIG doses per year	17.3	The 3-week dosing interval
IVIG g/kg per yr	6.93	
Price of IVIG per g	£69.00	BNF Accessed 04/02/2025: Gammagard S/D 10g powder and solvent for solution for injection bottles. Takeda UK Ltd. Active ingredients - Normal immunoglobulin human 10 gram. NHS indicative price £690
Cost of IVIG per kg per yr	£478.40	Note no allowance for drug pack wastage
25th percentile of population growth curve used to estimate the actual dose by age.		

	Yr	**Proportion SCID patients**
IVIG Use over time	1	100%
	3	59%
	8	0%

3.10 Model functionality

The model offers the functionality described in Table 24 in terms of optional settings for analysis.

Table 24 Model functionality

General setting	**Value**	**Options**
Model mode (0=deterministic; 1=PSA)	0	0, 1
Discount rate (costs)	3.5%	1.5%, 3.5%, 5%
Discount rate (effects)	3.5%	1.5%, 3.5%, 5%
ICER Threshold	£30,000	>= 0
Replicates (number of runs for the probabilistic analysis)	10000	>= 0
Max CEAC threshold	£200,000	>= 0
Increase CEAC threshold	£1,000	>= 0
Screening setting	**Value**	**Parameter name**
Screening algorithm	3	1, 2, 3
SCID birth prevalence (Country)	UK	England, Wales, Scotland, N Ireland, UK
Model specific setting	**Value**	**Parameter name**
Proportion of female in all population	0.5	0-1

Utility age adjustment	Adjusted	Adjusted, Not adjusted
Model population	UK 2022	England 2022, Wales 2022, Scotland 2022, N Ireland 2022, UK 2022, 100000, The Evaluation (IIVD)
Analysis setting	**Value**	**Parameter name**
Screening effectiveness (True – use the Evaluation survival data, FALSE – assume screening survival = family history)	TRUE	True, False
Screening effectiveness - FH Prior sample size adjustment	0.5	0 – 1
Proportion of test costs allocated to SCID	1	0 – 1
Use Evaluation costs for screen detected (FALSE = assume as family history)	TRUE	True, False
Include GT for X-linked SCID	FALSE	True, False
Include licensed GT therapy cost (Milan) (FALSE = Use generic DT costs for GT)	FALSE	True, False
Test sensitivity estimate - literature review sample size adjustment	0.75	0 – 1
ERT duration model	FALSE	True, False

3.11 Primary model analyses

The model can be run in deterministic, for development and validation, or probabilistic mode. All outputs reported are generated from probabilistic analyses. The model analyses are undertaken from an NHS perspective and over a lifetime horizon. Model outputs are reported for the following categories:

SCID cases: The model outputs the number of SCID cases by route of detection, together with the numbers of definitive treatments undertaken and mortality impacts.

Non-SCID results: The model predicts the number of babies that will receive a non-SCID screen positive result due to screening for SCID including false positives and non-SCID TCL results.

Disaggregated discounted cost and QALY outcomes: The model differentiates between QALY outcomes for patients and for parents. Cost outcomes are broken down into screening and diagnosis costs, first year management costs, including definitive treatments and discounted costs for 2 years and beyond.

Economic outcomes: The model generates standard health economic outputs comparing screening for SCID with no screening. The outputs include the absolute and incremental total and discounted costs and QALYs for the select population, together with the cost effectiveness plane and cost effectiveness acceptability curve.

4 Health economic modelling results

4.1 Baseline results

The annual number of babies with positive SCID screening result in a UK population is presented in Table 25 and the impact on presentation route, definitive treatment and mortality is presented in Table 26. Screening is estimated to provide early detection for between 11 and 15 cases of SCID per year compared to 3 (95% CI: 2, 4) babies being detected early by family history without screening. It is predicted that 0.3 (95% CI: 0, 0.8) SCID cases may be missed by screening, or one case missed every 3 (95% CI: 1, 50) years.

However, screening with the IIVD SCID technology, using the optimised algorithm (algorithm 3 in the Evaluation analyses) is also predicted to result in between 35 and 68 babies receiving a false positive result annually that would be identified at flow cytometry.

A further 65 patients (29, 116) will be expected to receive a non-SCID TCL result and require further follow-up and investigation. Of these babies 15 (5, 30) might be expected to be diagnosed with syndromes or non-SCID TCL secondary to other conditions that might have been expected to arise symptomatically in the absence of screening.

In 4 (1, 11) of the babies investigated for non-SCID TCL this might be expected to resolve spontaneously during follow-up, at a maximum of the Evaluation follow-up period. A similar number of babies, 4 (1, 11) might be expected to have persistent idiopathic non-SCID TCL. If follow-up investigation in practice is similar to that undertaken within the Evaluation, then it is estimated that approximately 41 (22, 65) babies and their parents will have some level of investigation triggered by screening that is inconclusive. It is estimated that in 18 (9, 28) of these cases the baby will have died shortly after birth.

(Note extended follow up after lockdown of the SCID Evaluation data has resulted in reclassification of some of the non-SCID TCL positive screening results. The principal impacts have been a reduction in the number of babies with a screen positive result classified as 'inconclusive'. See further details in the SCID Evaluation Final Report)

Table 25 Patients with SCID screen positive results

UK 2022 population, SCID screen positive babies	Mean	LCI	UCI
Total SCID patients	**12.7**	**10.8**	**14.8**
Patients with a false positive result	49.8	34.5	67.8
Total non-SCID TCL results	64.5	29.2	115.7
Syndromic TCL	10.3	4.1	19.0
Non-Syndromic TCL	4.4	0.9	10.7
Reversible TCL	4.4	0.9	10.7
Idiopathic TCL	4.4	0.8	10.4
Inconclusive TCL - Alive	23.5	13.3	36.5

Inconclusive TCL - Died	17.6	9.1	28.4
Screening algorithm: A = 10, B = 6, C = 1.08			

Screening is predicted to have a minimal impact on the distribution of definitive treatments between HSCT, GT and TT, though as presented in Table 22, the average age of definitive treatment is expected to reduce from approximately 10 months for those who would have otherwise been diagnosed symptomatically to approximately 4 months if screen detected. Improved management following early detection is estimated to lead to one (1, 2) avoided SCID deaths at 12 months of age per annual cohort and between 1 and 3 avoided deaths at 10 years of age.

Table 27 presents the disaggregated costs and QALY outcomes associated with screening compared to no screening. Patient QALYs include both the mortality benefits arising from avoided SCID deaths and utility gains associated with improved management following early detection. Screening is predicted to deliver 56 (10, 96) additional SCID patient QALYs discounted over the lifetime of an annual UK SCID cohort. Parental quality of life impacts included within the model include the adverse effects of receiving a false positive result from the baby's SCID screening test, a proxy assessment of uncertainties associated with a subset of the non-SCID TCL results, together with an assessment of parental bereavement impacts following infant death. The total QALY impact of screening on an annual cohort of parents is a loss of 1 (loss 9, gain 4) QALYs, indicating that on average the total QALYs lost through diagnostic uncertainty consequent on screening in the cohort are greater than the QALYs gained through avoided bereavement, reflecting the larger number of parents affected.

The incremental costs of screening and subsequent diagnostic investigations are estimated at approximately £5.3m per year. Early detection and improved management of an annual cohort of SCID patients is estimated to save approximately £419k (£102k, £749k) in the first year and an additional £38k (-£369k, £438k) discounted over the lifetime of the annual cohort. The incremental total discounted cost of screening is therefore estimated at £4.8m (£4.3m, £5.4m) per year.

The primary economic outcomes for screening compared to no screening for a UK 2022 population are presented in Table 28, together with the cost effectiveness plane and CEAC in Figure 15 and Figure 16 respectively.

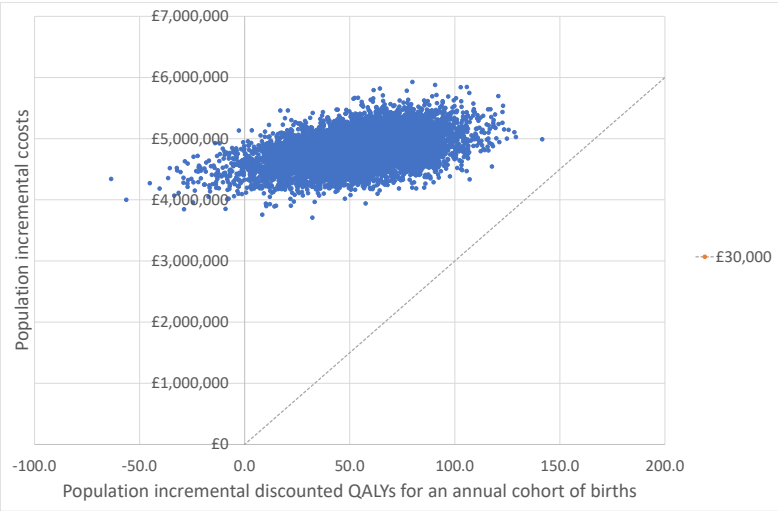


Figure 15 Cost effectiveness plane for screening versus no screening, baseline analysis.

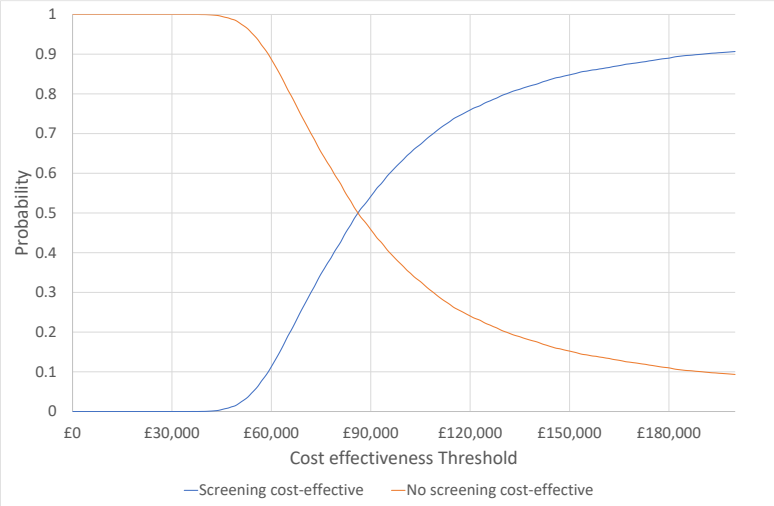


Figure 16 CEAC SCID screening compared to no screening, baseline analysis

Screening for SCID is predicted to deliver 163 (14, 288) additional life years for an annual cohort of SCID patients and a total discounted gain of 55 (5, 97) QALYs per annual screening cohort compared to no screening.

The cost effectiveness of screening for SCID compared to no screening is estimated at £87,813 per QALY gained. The UK 2022 population net monetary benefit of screening compared to no screening at a cost effectiveness threshold of £30,000 per QALY is -£3.2m (-£4.5m, -£2.0), this together with the cost effectiveness plane and CEAC demonstrates the degree of economic uncertainty in these results.

Table 26 SCID cases, definitive treatments and mortality

UK 2022 population, SCID cases	Screening			No Screening			Incremental		
	Mean	LCI	UCI	Mean	LCI	UCI	Mean	LCI	UCI
Total SCID	**12.7**	**10.8**	**14.8**	**12.7**	**10.8**	**14.8**	**0.0**	**0.0**	**0.0**
Screening detected	12.5	10.5	14.5	0.0	0.0	0.0	12.5	10.5	14.5
Symptomatically detected	0.2	0.0	0.6	9.5	7.9	11.3	-9.3	-11.1	-7.7
Family history detected	0.1	0.0	0.2	3.2	2.3	4.3	-3.2	-4.2	-2.2
HSCT	10.3	8.4	12.2	10.1	8.4	11.9	0.1	-0.7	0.7
GT	1.0	0.5	1.7	1.0	0.5	1.6	0.0	-0.1	0.1
TT	1.2	0.7	1.9	1.2	0.6	1.9	0.0	-0.1	0.1
Death pre DT	0.3	0.0	1.2	0.4	0.1	1.0	-0.2	-0.8	0.9
1 Year mortality	0.7	0.1	2.1	1.6	0.9	2.5	-0.9	-2.1	0.6
10 Year mortality	1.8	0.6	3.6	3.2	2.2	4.4	-1.4	-3.1	0.5

Table 27 Disaggregated discounted cost and QALY outcomes

UK 2022 population, Costs and QALYs	Screening			No Screening			Incremental		
	Mean	**LCI**	**UCI**	**Mean**	**LCI**	**UCI**	**Mean**	**LCI**	**UCI**
Total QALYs	**277.5**	**218.9**	**335.9**	**222.6**	**181.6**	**266.6**	**55.0**	**5.4**	**96.8**
Patient QALYs	283.5	226.1	341.1	227.1	186.5	271.2	56.3	10.0	95.9
Parental QALYs	-5.9	-13.3	-1.2	-4.6	-6.4	-3.1	-1.3	-8.8	3.6
Total costs	**£9,871,901**	**£8,955,792**	**£10,930,895**	**£5,042,363**	**£4,124,852**	**£6,116,040**	**£4,829,538**	**£4,301,992**	**£5,354,523**
Screening and diagnostic costs	£5,298,862	£5,253,894	£5,353,974	£12,106	£10,300	£14,078	£5,286,757	£5,241,856	£5,341,814
First year SCID management	£2,493,044	£1,918,273	£3,213,820	£2,911,714	£2,300,461	£3,685,681	-£418,670	-£749,403	-£102,442
Year 2+ SCID costs	£2,079,994	£1,587,192	£2,651,873	£2,118,543	£1,681,654	£2,621,988	-£38,549	-£438,325	£368,514
Scenario	Discount rate, QALYs: 3.5% Discount rate, costs: 3.5%			Screening algorithm: A = 10, B = 6, C = 1.08					

Table 28 Economic outcomes of screening for SCID compared to no screening

UK 2022 population, lifetime effects	Screening			No Screening			Incremental		
	Mean	**LCI**	**UCI**	**Mean**	**LCI**	**UCI**	**Mean**	**LCI**	**UCI**
Life years gained	877.0	694.7	1056.0	714.0	585.2	851.7	162.9	14.2	288.2
QALYS	781.7	615.5	946.6	607.1	495.2	727.2	174.6	36.0	292.3
Costs	£12,973,861	£11,356,025	£14,836,768	£7,561,233	£6,131,468	£9,205,288	£5,412,628	£4,485,407	£6,293,625
Discounted QALYS	277.5	218.9	335.9	222.6	181.6	266.6	55.0	5.4	96.8
Discounted Costs	£9,871,901	£8,955,792	£10,930,895	£5,042,363	£4,124,852	£6,116,040	£4,829,538	£4,301,992	£5,354,523
NMB at £30000 per QALY	-£1,545,404	-£2,888,294	-£288,064	£1,634,187	£764,352	£2,478,068	-£3,179,590	-£4,465,078	-£2,003,917
Incremental cost effectiveness							£87,813		
Probability that screening dominates no screening							0%		
Probability screening is dominated by no screening							2%		
Scenario	Discount rate, QALYs: 3.5%			CE Threshold: £30000					
	Discount rate, costs: 3.5%			Screening algorithm: A = 10, B = 6, C = 1.08					

4.2 Scenario analysis

4.2.1 Birth prevalence sensitivity analysis and the Four Nations

The retrospective data suggests that SCID birth prevalence in the English population is higher than in the three other nations. Table 29 presents the economic analysis summary statistics for the Four Nation 2022 populations, based on the SCID birth prevalences presented in Table 2 and Figure 5, Figure 17 presents the CEAC for the respective birth prevalences.

This analysis also demonstrates the impact of birth prevalence on the economics of SCID screening. Thus, for instance the SCID birth prevalence in the Evaluation period was approximately 1.2 per 100,000 births, which is lower than the average birth prevalence over the previous 10 years. If this is indicative of a downward trend in SCID birth prevalence rather than random variation, then the economics of screening are likely to deteriorate over time.

Table 29 Incremental population lifetime effects for the four nation populations

	Northern Ireland 2022	**Wales 2022**	**Scotland 2022**	**England 2022**
Births 2022	**20837**	**28296**	**46959**	**577046**
Birth prevalence per 100,000	**0.76**	**1.38**	**1.67**	**1.96**
Incremental cost per QALY	£256,408	£126,904	£102,055	£85,057
Probability that screening dominates no screening	0.00%	0.00%	0.00%	0.00%
Probability screening is dominated by no screening	9%	2.4%	1.9%	1.6%

Figure 17 SCID screening CEACs for different birth prevalences

4.2.2 Impact of discounting on cost effectiveness

Table 30 presents the impact of different discount rates on the cost effectiveness of screening for SCID. Reducing the discount rate of both costs and QALYS from 3.5% to 1.5% improves the cost effectiveness of screening from the baseline £88,100 to £51,600 per QALY gained, whilst increasing discount rate to 5% pushes the cost effectiveness out to £121,900 per QALY gained.

Table 30 Impact of different discount rates on economic outcomes

Discount rate, QALYs	**0%**	**1.50%**	**3.50%**	**5%**	**1.50%**
Discount rate, costs	**0%**	**1.50%**	**3.50%**	**5%**	**3.5%**
Discounted QALYS	174.6	98.5	55.0	39.4	98.5
Discounted Costs	£5,412,628	£5,025,675	£4,829,538	£4,760,707	£4,825,154
NMB at £30000 per QALY	-£174,174	-£2,069,512	-£3,179,590	-£3,578,769	-£1,868,991
Incremental cost effectiveness	£30,997	£51,002	£87,813	£120,836	£48,967

4.2.3 Enzyme replacement therapy differential usage analysis

Based upon clinical opinion and an absence of a significant difference in the average duration of ERT usage in ADA SCID patients in the retrospective data the baseline analysis assumes that average ERT usage will be unaffected by screen detection.

However, Section 3.9.6 demonstrates that the retrospective SCID data also shows an association between the age at first definitive treatment (DT) and ERT usage. Furthermore, the retrospective and SCID Evaluation data also show that the average age of first DT varies by mode of detection, with

screening reducing the age of first DT to 4 months from 10 months for symptomatic detection. Table 31 presents the impact of assuming that screening will reduce the average ERT usage in line with the suggested impact on age at first DT. It can be seen that if screening reduces ERT usage then the first year cost saving associated with screening will increase from £419k to £679k, leading to an improvement in cost effectiveness from £87,800 to £83,000 per QALY gained.

Table 31 Impact of assuming that early detection reduces the average duration of ERT usage

UK 2022 population, lifetime effects	Incremental effects of screening compared to no screening	
	Baseline analysis	**ERT duration model**
Discounted QALYS	55.0	55.1
Screening and diagnostic costs	£5,286,757	£5,286,578
First year SCID management	-£418,670	-£679,106
Year 2+ SCID costs	-£38,549	-£35,772
Discounted Costs	4829537.7	4571701.0
NMB at £30000 per QALY	-£3,179,590	-£2,919,071
Cost per QALY gained	£87,813	£82,990

4.2.4 Apportionment of laboratory test costs of screening between SCID and SMA

As described in section 3.9.2 the screening technology assessed in this report has the capability and functionality to detect both SCID and SMA. The apportionment of the fixed and operating laboratory costs between the two conditions has the potential to impact on the economics of screening for either. The baseline economic analysis assumes that all the laboratory costs of screening are allocated to SCID. If screening is undertaken for both SMA and SCID then apportionment of the laboratory costs of screening needs to be considered.

This sensitivity analysis examines two alternative approaches to apportioning the cost of the screening. Firstly, the marginal impact of screening for SCID+SMA compared to screening for SMA alone is considered, that is 10% of the laboratory cost of screening. Secondly, apportioning of costs according to the relative birth prevalence of the two conditions is considered. Since this analysis only impacts on the costs of screening the other SCID management cost components and QALY outcomes are unaffected. The economic outcomes are presented in Table 32 and the CEAC for the two approaches is presented in Figure 18.

The cost effectiveness of screening for SCID in these two scenarios are estimated at £4,409 and £8,062 per QALY gained respectively and the probability that it is cost effective at a threshold of £30,000 is 98% and 97% respectively.

Table 32 Economic outcomes, minimal marginal cost of SCID testing

UK 2022 population, lifetime effects		
Apportionment method	**Minimal marginal cost**	**Relative birth prevalence**
Proportion of screening lab costs	**10%**	**14%**
Incremental cost effectiveness	£4,409	£8,062
Probability that screening dominates no screening	17%	4%
Probability screening is dominated by no screening	0%	1%
Probability CE better than £30,000	98%	97%
Discount rate, QALYs: 3.5% Discount rate, costs: 3.5%	Screening algorithm: A = 10, B = 6, C = 1.08	

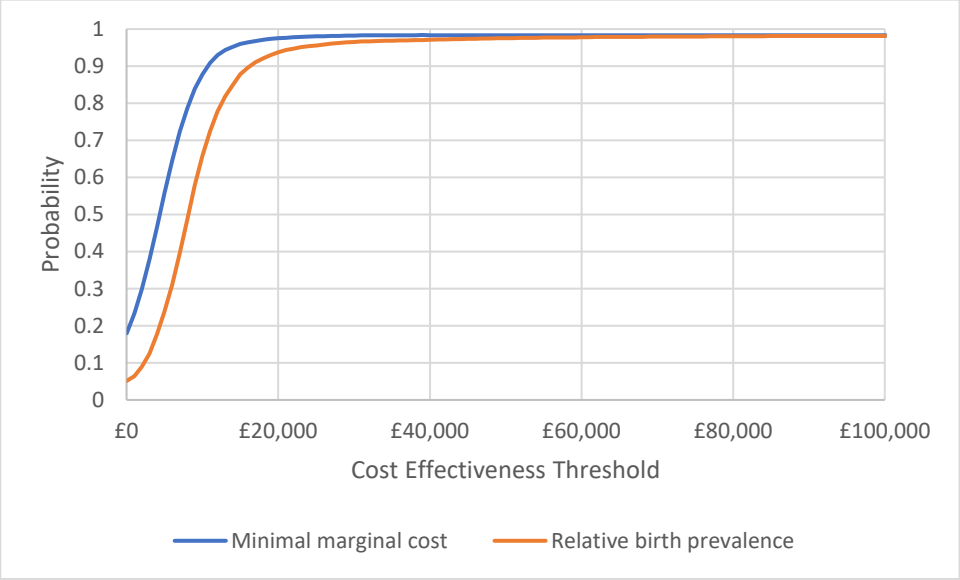


Figure 18 CEACs for different approaches to allocating costs of screening

4.2.5 Assumptions regarding estimation of screen detection survival

Table 33 explores the impact of different approaches to estimating survival in screen detected patients in the Model. Previous modelling of SCID screening has assumed that survival following screen detection has been equivalent to survival following family detection. The Evaluation provides the first direct UK evidence on survival following screen detection, however as Figure 8 demonstrates the sample size is small and survival is uncertain.

Rather than either relying wholly on the Evaluation screening data, or wholly on the previous family history assumption, the Model analysis uses a Bayesian updating approach to estimate survival following screen detection.

The sample size adjustment parameter determines the weighting given to our prior belief that survival following screen detection would be similar to family history survival. Table 33 demonstrates that if we just rely on the Evaluation data the uncertainty in the QALYs gained estimate is large varying from -23.5 to 96.4 and significantly crosses 0. However, relying solely on prior family history assumptions, apart from being wasteful of the Evaluation data, may overstate the average benefit of screen detection and overstate our certainty in the effectiveness of screen detection.

Table 33 Assumptions regarding estimation of screen detection survival

UK 2022 population, lifetime effects	Assuming survival following screen detection is equivalent to family history			Baseline (sample size adjustment of 50% for FH prior)			Use screen detection survival from the Evaluation (sample size adjustment of 10% for FH prior)		
	Mean	**LCI**	**UCI**	**Mean**	**LCI**	**UCI**	**Mean**	**LCI**	**UCI**
Life years gained	179.6	44.6	296.5	162.9	14.2	288.2	136.6	-73.9	286.9
QALYS	189.7	63.5	303.5	174.6	36.0	292.3	150.4	-42.7	291.9
Costs	£5,499,979	£4,641,404	£6,323,830	£5,412,628	£4,485,407	£6,293,625	£5,279,379	£4,013,077	£6,269,843
Discounted QALYS	60.5	16.9	99.9	55.0	5.4	96.8	46.2	-23.5	96.4
Discounted Costs	£4,857,890	£4,351,897	£5,372,216	£4,829,538	£4,301,992	£5,354,523	£4,789,398	£4,176,291	£5,348,585
NMB at £30000 per QALY	-£3,042,485	-£4,205,192	-£1,902,651	-£3,179,590	-£4,465,078	-£2,003,917	-£3,404,232	-£5,106,893	-£2,033,251
Incremental cost effectiveness	£80,278			£87,813			£103,729		

5 Discussion and Conclusions

5.1 Discussion

The objective of this work was to update the health economic model that was used by the UK NSC to support its consideration of screening for SCID in 2016/17 to account for changing evidence in the domain. The overall structure of the new model is similar to the previous model (7) with the additional inclusion of parental impacts, including an improved modelling of false positive and bereavement effects, and an update of the parameters in the model in line with new evidence. Despite these similarities in model structure the cost effectiveness of screening for SCID has gone £18,222 per QALY gained in the original analysis to £87,813 here.

A factor giving rise to this change in the economic attractiveness of screening for SCID is the improvement in SCID diagnosis and management in recent years. The original model used UK SCID survival evidence reported by Brown et al in 2011 (40) that was based upon SCID cases diagnosis and management over the period 1982 to 2010. Improvements in SCID management and treatment patterns means that mortality of symptomatically diagnosed SCID patients has improved from approximately 60% in the period covered by the Brown study to approximately 30% in the NUTH/GOSH retrospective cohort over the period 2010-2020. This improvement in survival of symptomatically detected cases means that the potential benefit from screening has reduced markedly. In parallel to this, changes in the costs of screening and management and their inclusion in the model have also contributed to the position.

It is noteworthy that the NHS SCID Evaluation has provided the first direct UK evidence regarding SCID survival following screen detection. This is an important move forward in the SCID evidence, even though numbers are still small.

A major consideration for the UK NSC in establishing the SCID Evaluation was the high potential false positive rate for SCID and the large number of babies that might be identified with non-SCID TCL by the Perkin Elmer Enlite screening technology and the high levels of uncertainty associated with relying on international evidence. The SCID Evaluation has been successful in providing improved, direct UK evidence on these rates. Specifically, the current generation of real time PCR based SCID screening technologies implemented in the SCID Evaluation, principally IIVD, have demonstrated improvements in the false positive rate for SCID with improved levels of certainty.

In contrast the number of idiopathic non-SCID TCL experienced in the SCID Evaluation is in line with the original SCID model predictions in 2016/17. In this case the Evaluation, again, provides important direct, improved evidence, being based on the England population and practice rather than Californian experience. However, the Evaluation has also introduced a new category of 'inconclusive' that was not in the original assessment and arose during the course of the Evaluation in light of a mixture of practical and claimed ethical difficulties with ensuring data completeness, diagnostic completeness and deaths prior to a confirmed diagnosis being reached. This is potentially a large category of patients for whom there may still be uncertainty as to the impact of screening.

There have been major improvements in the evidence for estimating the HrQoL impacts of screening for SCID. Regarding the utility impacts on SCID patients, both the HrQoL utility mapping algorithms and UK SCID PEDSQL Newcastle data collected by Abd Hamid represent major improvements in key evidence. The Model analysis therefore no longer relies on proxy assessment or QALY assumptions, the SCID patient utility estimates therefore have a much improved credibility with a better

representation of uncertainty. This is possibly the best implementation of SCID patient utilities in all the currently the available SCID models.

Similarly, this analysis is the first economic analysis of SCID screening to include parental impacts, with the outcomes research study (2) improving the evidence on the effects of false positive results. This evidence confirms that there is an impact on parents HrQoL utilities, however these are small and where measurable are time limited. This new evidence reduces the structural uncertainty in this issue that may help to resolve the discussion. Similarly, the improved evidence concerning parental bereavements demonstrates a measurable impact, that it has been possible to include within the model, though of course the improvements in SCID survival without screening have moderated the importance of this for screening economics. Whilst there were insufficient patients recruited in the outcomes research to provide good comparative quantitative evidence, there was qualitative evidence suggesting potentially sustained impacts from unresolved parental certainties associated with non-SCID TCL results.

The Model has attempted to include some measure of the costs and QALY impacts for babies with non-SCID TCL and inconclusive findings from screening, though there remains uncertainty in this issue. Whilst the economic evidence, such as it is, suggests that these impacts are unlikely to affect economic decision uncertainty for SCID, minimising these effects may remain an issue for future evidence collection and practice development.

The acquisition of HES data was a substantial undertaking both in terms of the effort involved for the Evaluation team and the time it took to obtain, with HES data only arriving at the very end of the Evaluation analysis period despite many months of preparation. However, this data has been a game changer for the economic evaluation of SCID in England. There are two things to note. Firstly, evidence infrastructure developments for enabling timely access should be a priority for improving the utilisation of HES data early in the newborn screening modelling process. Secondly, arriving when it did, the current analysis has far from exhausted the evidence potential of this data source for SCID.

For instance, this is the first evidence to include data on the diagnostic journey of SCID patients up to the point of referral to a specialist SCID treatment centre. This has not been separated out in the current analysis, purely because of time constraints on the analysis, though the none GOSH/NUTH costs are included in costs. It would be a simple and interesting additional analysis to undertake.

Where it has been possible to validate the HES data against the data from the retrospective cohort, the picture is mixed. Length of stay data at NUTH and GOSH matched well with HES data, with some variation possibly associated with classification of day case activity. In contrast, the identification of definitive treatment spells is difficult in HES potentially due to issues with coding, the analysis therefore relied on the retrospective data. HES / ONS data added useful information to follow-up and survival, with HES data including activity at sites other than GOSH and NUTH that extended follow-up for some individuals, conversely follow-up contacts in the retrospective data for some patients extended follow-up beyond that implied by HES, hence in this case the two sources were mutually beneficial. The Kaplan Meier survival analyses took the maximum date of last follow-up.

5.2 Conclusions

Taken on its own the cost effectiveness of screening for SCID compared to not screening is in the order of £80-90k per QALY gained when costs and QALYS are discounted at 3.5%. This is higher than

economic thresholds typically implemented in the UK. Furthermore, the combined parametric uncertainty captured in the Model is such that the 95% confidence interval for the incremental net monetary benefit of screening is wholly negative. Whilst approaches to discounting have the potential to impact on the economics of screening for SCID, the above conclusions are robust to all the discounting scenarios considered in this report.

It is notable that the economics of screening for SCID have deteriorated since the economic evaluation that was undertaken prior to the Evaluation.(7) The principle causes of this shift are firstly, the improvements in management and survival of SCID patients that have taken place over recent years, that undermines the potential benefits of screening and secondly the increased costs associated with the latest generation of SCID screening technologies.

The cost effectiveness of screening for SCID is highly dependent on the birth prevalence, with the economics of screening deteriorating with lower levels of birth prevalence. There are two issues arising. Firstly, the SCID birth prevalence within the period of the Evaluation was lower than the average used in the model. If this lower birth prevalence is evidence of a trend towards lower levels of SCID then screening will become less cost effective than estimated here. Secondly, there is evidence of high levels of geographical (as a proxy for other factors) variation in the birth prevalence of SCID. This report demonstrates that the economics of screening for SCID may vary between the four UK Nations that all demonstrate lower SCID birth prevalence than England.

The latest generation of SCID screening technologies, including the IIVD and Revvity products included within the SCID Evaluation, also provide the facility to screen for SMA within the same screening laboratory process. How the laboratory costs of screening are apportioned between the two rare conditions has a crucial impact on the economics of screening for SCID. This analysis has examined the minimum marginal cost of screening for SCID + SMA compared to screening for SMA alone. This analysis reverses the economics of screening for SCID, with an average cost effectiveness of £8,000 per QALY gained.

This modelling study has identified and included the parental impacts of screening for SCID. The SCID Evaluation and associated outcomes research study have been successful in addressing uncertainties in the number and impact of false positive results generated by SCID screening that were an issue in the 2016/17 UK NSC consideration. The new generation IIVD test implemented in the SCID Evaluation gives rise to fewer false positives than the previous SCID screening technology. The SCID outcomes research identified and estimated the negative impact of these babies' false positives results on parental quality of life.

There are significant remaining uncertainties in the performance of the SCID screening technologies with regard to the number of incidental, non-SCID TCL and inconclusive findings that are generated. However, given that the parental QALY impacts identified are an order of magnitude smaller than the direct QALY benefits to babies, it is unlikely that these uncertainties will impact on the economics of screening. Thus, while managing and minimising incidental findings from SCID screening may be an area for further research and screening development, this is not primarily an economic issue.

6 References

1. NHS SCID Evaluation Oversight Group. Evaluation of Screening for Severe Combined Immunodeficiency (SCID). Final Report. London: NHSE; 2025.
2. Chudleigh J, Holder P, Musa C, Moody L, Olander E, Dixon S, et al. Exploring parents' & health professionals' experiences of the introduction of Severe Combined Immunodeficiency (SCID) into the Newborn Screening Programme: a research project undertaken in parallel with the NHS Evaluation of screening for SCID. London: King's College London; 2024.
3. Hardin O, Lokhnygina Y, Buckley RH. Long-Term Clinical Outcomes of Severe Combined Immunodeficiency Patients Given Nonablative Marrow Transplants. J Allergy Clin Immunol Pract. 2022;10(4):1077-83.
4. Hamid IJA. Clinical, Immunological and Psycho-Social Outcome of SCID Patients Who underwent Hematopoietic Stem Cell Transplantation in Newcastle, UK, 1987 – 2012 and Long-term Outcome of the UK SCID Cohort. Newcastle: Newcastle University; 2017.
5. Kelly CB, Soley-Bori M, Lingam R, Forman J, Cecil L, Newham J, et al. Mapping PedsQL™ scores to CHU9D utility weights for children with chronic conditions in a multi-ethnic and deprived metropolitan population. Quality of Life Research. 2023;32(7):1909-23.
6. Camacho EM, Gold KJ, Murphy M, Storey C, Heazell AEP. Measuring EQ-5D-5L utility values in parents who have experienced perinatal death. The European Journal of Health Economics. 2024;25(8):1383-91.
7. Bessey A, Chilcott J, Leaviss J, de la Cruz C, Wong R. A Cost-Effectiveness Analysis of Newborn Screening for Severe Combined Immunodeficiency in the UK. International Journal of Neonatal Screening 2019;5(3):28.
8. Ding Y, Thompson JD, Kobrynski L, Ojodu J, Zarbalian G, Grosse SD. Cost-Effectiveness/Cost-Benefit Analysis of Newborn Screening for Severe Combined Immune Deficiency in Washington State. The Journal of Pediatrics. 2016;172:127-35.
9. Van der Ploeg CPB, Blom M, Bredius RGM, van der Burg M, Schielen P, Verkerk PH, et al. Cost-effectiveness of newborn screening for severe combined immunodeficiency. Eur J Pediatr. 2019;178(5):721-9.
10. van den Akker-van Marle ME, Blom M, van der Burg M, Bredius RGM, Van der Ploeg CPB. Economic Evaluation of Different Screening Strategies for Severe Combined Immunodeficiency Based on Real-Life Data. International Journal of Neonatal Screening 2021;7(3):15.
11. Shih STF, Keller E, Wiley V, Wong M, Farrar MA, Chambers GM. Economic Evaluation of Newborn Screening for Severe Combined Immunodeficiency. International Journal of Neonatal Screening 2022;8(3):20.
12. Shih STF, Keller E, Wiley V, Farrar MA, Wong M, Chambers GM. Modelling the Cost-Effectiveness and Budget Impact of a Newborn Screening Program for Spinal Muscular Atrophy and Severe Combined Immunodeficiency. International Journal of Neonatal Screening 2022;8(3):20.
13. Thomas C, Durand-Zaleski I, Frenkiel J, Mirallie S, Leger A, Cheillan D, et al. Clinical and economic aspects of newborn screening for severe combined immunodeficiency: DEPISTREC study results. Clin Immunol. 2019;202:33-9.
14. South E, Cox E, Meader N, Woolacott N, Griffin S. Strimvelis^R for Treating Severe Combined Immunodeficiency Caused by Adenosine Deaminase Deficiency: An Evidence Review Group Perspective of a NICE Highly Specialised Technology Evaluation. Pharmacoeconom Open. 2019;3(2):151-61.
15. Westwood ME, Emerson J, Armstrong N, Stirk L. Newborn screening for severe combined immunodeficiency (SCID) in the NHS Newborn Blood Spot (NBS) screening programme: A rapid evidence review. External review against programme appraisal criteria for the UK National

Screening Committee (NSC), prepared by Kleijnen Systematic Reviews Ltd.: The UK National Screening Committee; 2024.
16. Booth NA, Freeman CM, Wright BL, Rukasin C, Badia P, Daines M, et al. Severe Combined Immunodeficiency (SCID) Screening in Arizona: Lessons Learned from the First 2 Years. J Clin Immunol. 2022;42(6):1321-9.
17. Heather N, de Hora M, Brothers S, Grainger P, Knoll D, Webster D. Introducing Newborn Screening for Severe Combined Immunodeficiency-The New Zealand Experience. International Journal of Neonatal Screening 2022;8(2):10.
18. Lev A, Sharir I, Simon AJ, Levy S, Lee YN, Frizinsky S, et al. Lessons Learned From Five Years of Newborn Screening for Severe Combined Immunodeficiency in Israel. J Allergy Clin Immunol Pract. 2022;10(10):2722-31.e9.
19. Puck JM, Gennery AR. Establishing Newborn Screening for SCID in the USA; Experience in California. International Journal of Neonatal Screening 2021;7(4):31.
20. Eissa H, Thakar MS, Shah AJ, Logan BR, Griffith LM, Dong H, et al. Posttransplantation late complications increase over time for patients with SCID: A Primary Immune Deficiency Treatment Consortium (PIDTC) landmark study. Journal of Allergy and Clinical Immunology. 2024;153(1):287-96.
21. Thakar MS, Logan BR, Puck JM, Dunn EA, Buckley RH, Cowan MJ, et al. Measuring the effect of newborn screening on survival after haematopoietic cell transplantation for severe combined immunodeficiency: a 36-year longitudinal study from the Primary Immune Deficiency Treatment Consortium. Lancet. 2023;402(10396):129-40.
22. Lankester AC, Neven B, Mahlaoui N, von Asmuth EGJ, Courteille V, Alligon M, et al. Hematopoietic cell transplantation in severe combined immunodeficiency: The SCETIDE 2006-2014 European cohort. J Allergy Clin Immunol. 2022;149(5):1744-54.e8.
23. Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published Kaplan-Meier survival curves. BMC Medical Research Methodology. 2021;21(1):111.
24. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Sheffield: The University of Sheffield; 2011.
25. (ONS). Office for National Statistics. Statistical bulletin, National life tables – life expectancy in the UK: 2020 to 2022.: ONS website; 2024.
26. Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D Utility Scores from the PedsQL™ Generic Core Scales. PharmacoEconomics. 2014;32(7):693-706.
27. Lambe T, Frew E, Ives NJ, Woolley RL, Cummins C, Brettell EA, et al. Mapping the Paediatric Quality of Life Inventory (PedsQL™) Generic Core Scales onto the Child Health Utility Index–9 Dimension (CHU-9D) Score for Economic Evaluation in Children. PharmacoEconomics. 2018;36(4):451-65.
28. Mpundu-Kaambwa C, Chen G, Huynh E, Russo R, Ratcliffe J. Mapping the PedsQL™ onto the CHU9D: An Assessment of External Validity in a Large Community-Based Sample. PharmacoEconomics. 2019;37(9):1139-53.
29. Sweeney R, Chen G, Gold L, Mensah F, Wake M. Mapping PedsQLTM scores onto CHU9D utility scores: estimation, validation and a comparison of alternative instrument versions. Quality of Life Research. 2020;29(3):639-52.
30. Shafie AA, Chhabra IK, Wong JHY, Mohammed NS. Mapping PedsQL™ Generic Core Scales to EQ-5D-3L utility scores in transfusion-dependent thalassemia patients. The European Journal of Health Economics. 2021;22(5):735-47.
31. DeLuca EK. The Development of a Preference-Based Health-Related Quality of Life Measure for Children Based on the PedsQL: the PedsUtil Scoring System. Michigan: University of Michigan; 2023.
32. Petrou S, Morrell J, Spiby H. Assessing the empirical validity of alternative multi-attribute utility measures in the maternity context. Health and Quality of Life Outcomes. 2009;7(1):40.

33. Kind P. HG, Macran S. UK population norms for EQ-5D. York, UK: The University of York Centre for Health Economics; 1999.
34. Christensen H, Trotter CL, Hickman M, Edmunds WJ. Re-evaluating cost effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study. BMJ : British Medical Journal. 2014;349:g5725.
35. National Institute for Health and Care Excellence (NICE). Highly Specialised Technology Evaluation (HST7). Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency. 2018.
36. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance TA755. Risdiplam for treating spinal muscular atrophy. 2021.
37. Song J, Floyd FJ, Seltzer MM, Greenberg JS, Hong J. Long-Term Effects of Child Death on Parents' Health-Related Quality of Life: A Dyadic Analysis. Family Relations. 2010;59(3):269-82.
38. The University of Sheffield. Cost-effectiveness modelling of Newborn Screening for Spinal Muscular Atrophy. London: The UK National Screening Committee; 2025.
39. NHS England. 2021/22 National Cost Collection Data Publication. National Schedule of NHS Costs 2021/22. 2023.
40. Brown L, Xu-Bayford J, Allwood Z, Slatter M, Cant A, Davies EG, et al. Neonatal diagnosis of severe combined immunodeficiency leads to significantly improved survival outcome: the case for newborn screening. Blood. 2011;117(11):3243-6.

Appendix 1 Economic evidence for SCID screening published since 2016

Tables temporarily included as an embedded spreadsheet – To be transferred to open form.

Appendix 2: Mapping between Diagnostic Review Group and Model classifications

DRG classification and benefit	Count	Model classification
In H24, 1. Dis-benefit	3	Condition 11 - Inconclusive - alive - disbenefit
In H24, 4. Unknown	2	Condition 11 - Inconclusive - alive - disbenefit
In H26, 1. Dis-benefit	2	Condition 11 - Inconclusive - alive - disbenefit
In H26, 4. Unknown	1	Condition 11 - Inconclusive - alive - disbenefit
Inc D2, 1. Dis-benefit	2	Condition 11 - Inconclusive - alive - disbenefit
Inc D2, 4. Unknown	1	Condition 11 - Inconclusive - alive - disbenefit
Inc D3, 1. Dis-benefit	1	Condition 12 - Inconclusive - died - disbenefit
Inc D3, 2. No/Neutral benefit (+\-diagnosis but no benefit)	1	Condition 12 - Inconclusive - died - disbenefit
Inc D4, 1. Dis-benefit	3	Condition 12 - Inconclusive - died - disbenefit
Inc E8a, 1. Dis-benefit	3	Condition 11 - Inconclusive - alive - disbenefit
Inc E8d, 1. Dis-benefit	2	Condition 12 - Inconclusive - died - disbenefit
Inc F10, 2. No/Neutral benefit (+\-diagnosis but no benefit)	2	Condition 12 - Inconclusive - died - disbenefit
Inc F11, 1. Dis-benefit	3	Condition 12 - Inconclusive - died - disbenefit
Inc F17, 2. No/Neutral benefit (+\-diagnosis but no benefit)	1	Condition 12 - Inconclusive - died - disbenefit
Inc H12, 1. Dis-benefit	7	Condition 11 - Inconclusive - alive - disbenefit
Inc H14, 1. Dis-benefit	3	Condition 11 - Inconclusive - alive - disbenefit
Inc H14, 2. No/Neutral benefit (+\-diagnosis but no benefit)	1	Condition 11 - Inconclusive - alive - disbenefit
ITCL, 3b. Benefit (earlier diagnosis of non-SCID TCL)	2	Condition 1 - Idiopathic TCL - benefit
ITCL, 4. Unknown	2	Condition 2 - Idiopathic TCL - unknown
Non-syndr TCL, 1. Dis-benefit	1	Condition 8 - Non syndromes TCL - disbenefit
Non-syndr TCL, 2. No/Neutral benefit (+\-diagnosis but no benefit)	3	Condition 7 - Non syndromes TCL - no/neutral benefit
Non-syndr TCL, 3b. Benefit (earlier diagnosis of non-SCID TCL)	1	Condition 6 - Non syndromes TCL - benefit
Normal T-cell subset, 1. Dis-benefit	71	Normal T-cell subset
Normal T-cell subset, 2. No/Neutral benefit (+\-diagnosis but no benefit)	2	Normal T-cell subset
SCID, 2. No/Neutral benefit (+\-diagnosis but no benefit)	1	SCID

SCID, 3a. Benefit (earlier diagnosis of SCID)	6	SCID
Syndr wTCL, 3b. Benefit (earlier diagnosis of non-SCID TCL)	3	Condition 3 - Syndromes TCL - benefit
Syndrome wTCL, 1. Dis-benefit	1	Condition 5 - Syndromes TCL - disbenefit
Syndrome wTCL, 2. No/Neutral benefit (+\-diagnosis but no benefit)	2	Condition 4 - Syndromes TCL - no/neutral benefit
Syndrome wTCL, 3b. Benefit (earlier diagnosis of non-SCID TCL)	2	Condition 3 - Syndromes TCL - benefit
Syndrome wTCL, 3c. Benefit (earlier diagnosis of another condition)	1	Condition 3 - Syndromes TCL - benefit
TCL revers, 1. Dis-benefit	5	Condition 10 - Reversible TCL - disbenefit
Grand Total	141	

Appendix 3: Model categories for Screen positive cases

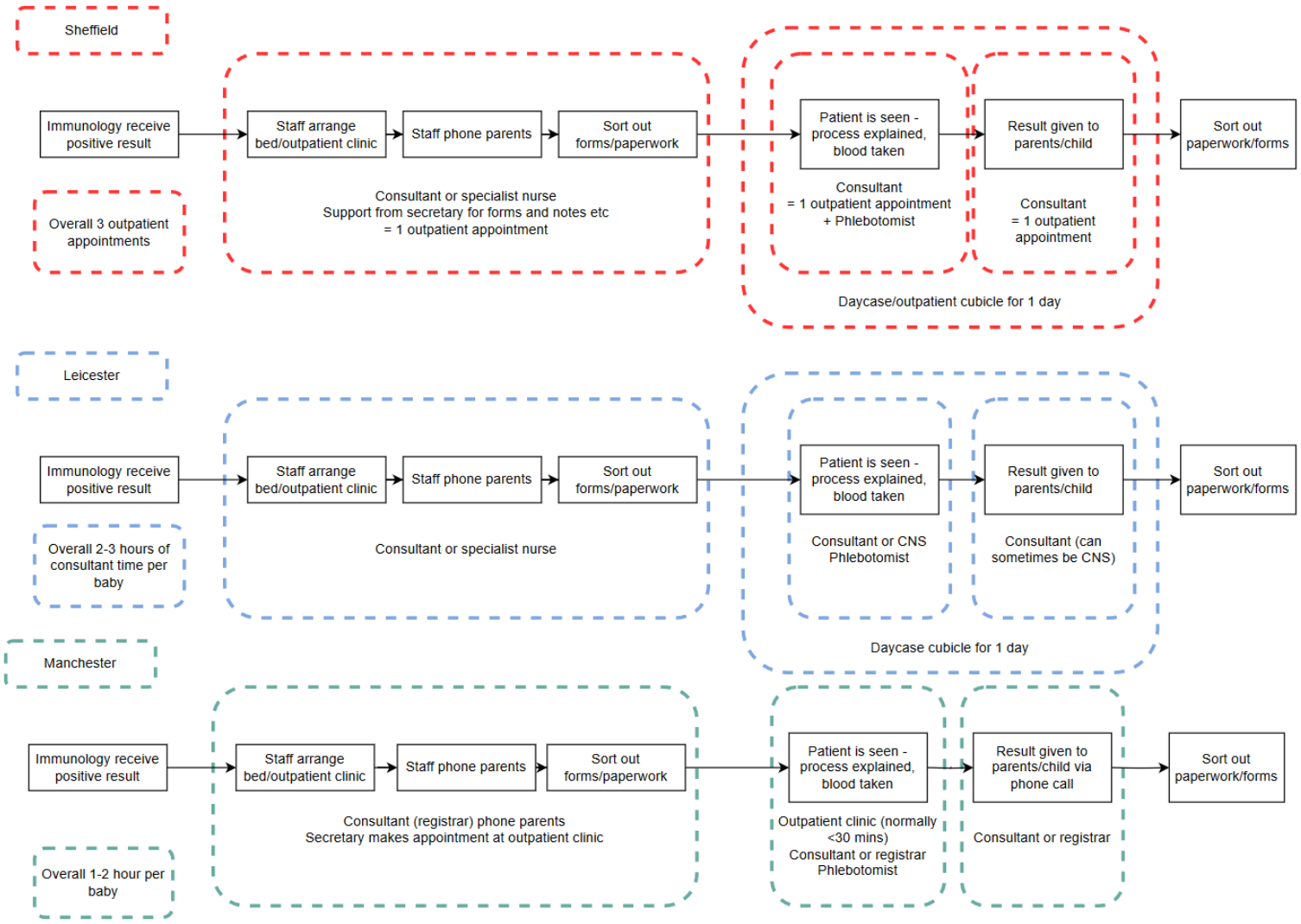
Major Category (Evaluation category if different)	**Model Category**	Evaluation Benefit category	Screening costs & flow cytometry confirmation costs	Follow up costs	Quality of Life impacts		Notes
					Patient	Parental	
SCID	**SCID Note: mortality differentiated by route to diagnosis.**	Benefit earlier diagnosis of SCID	Y	Y	Yes	Yes – decrement associated with death	Costs of treatment and long term outcomes included for all SCID patients
		No/Neutral benefit (+/- diagnosis but no benefit)	Y	Y	Yes	Yes – decrement associated with death	Costs of treatment and long term outcomes included for all SCID patients
False Positive (Normal T cell subsets at initial FC)	**False Positive – all disbenefit**	Disbenefit	Y	N	No	Yes – we will apply the decrement associated with a false positive result	No further follow up costs are included in the model
		No/Neutral benefit (+/- diagnosis but no benefit)	N/A	N/A	N/A	N/A	Not included in the model
Reversible TCL	**Reversible TCL – all disbenefit**	Disbenefit	Y	Y	No (Not included in model)	Yes – we will apply the decrement associated with a false positive result	The cost of the second flow cytometry and associated appointment is included in the model 1x Flow cytometry and 2x immunology outpatient appointment
		No/Neutral benefit (+/- diagnosis but no benefit)	N/A	N/A	N/A	N/A	Not included in the model

		Benefit - earlier diagnosis of non-SCID TCL	N/A	N/A	N/A	N/A	Not included in the model
Idiopathic TCL	**Idiopathic TCL – with benefit**	Benefit - earlier diagnosis of non-SCID TCL	Y	N - Not included	Possible benefit not included in model	Possible benefit not included in model	Example benefit is through avoidance of live vaccines in babies with significant immunocompromise.
	Idiopathic TCL – unknown possible disbenefit	Unknown (possible disbenefit)	Y	Y	No	Yes – we will apply the decremental associated with a false positive result as a proxy	The cost of the second flow cytometry, associated appointment and further testing is included in the model 1 x flow cytometry, 3 x immunology outpatient appointment, 1x genetic test (Primary immune deficiency syndromes 206 exome panel)
Syndromes with TCL	**Benefit - earlier diagnosis of non-SCID TCL**	Benefit - earlier diagnosis of non-SCID TCL	Y	N – Not included	Possible benefit not included in model	Possible benefit not included in model	For earlier diagnosis assume follow-up costs would have been incurred in the absence of screening – Concerns expressed by group that some of early diagnostic costs may be marginal.
	No/Neutral benefit (+/- diagnosis but no benefit)	No/Neutral benefit (+/- diagnosis but no benefit)	Y	N	No	No	Assume would have had further follow up in the absence of screening
	Unknown	Unknown	Y	N	No	No	Assume would have had further follow up in the absence of screening
	Benefit - earlier	Benefit - earlier	Y	N	Possible benefit not	Possible benefit not included in model	For earlier diagnosis assume follow-up costs would have been

Non-syndromic TCL	**diagnosis of non-SCID TCL**	diagnosis of non-SCID TCL			included in model		incurred in the absence of screening
	No/Neutral benefit (+/- diagnosis but no benefit)	No/Neutral benefit (+/- diagnosis but no benefit)	Y	N	No	No	Assume would have had further follow up in the absence of screening
	Disbenefit (Model neutral)	Disbenefit (Model neutral)	Y	N	No	Possible disbenefit not included in model	Assume would have had further follow up in the absence of screening
	Unknown	Unknown	Y	N	No	No	Assume would have had further follow up in the absence of screening
Inconclusive – Alive	**Disbenefit**	Disbenefit	Y	Y	No	Yes – we will apply the decremental associated with a false positive result as a proxy	Some follow-up costs will be included. 1 x flow cytometry, 3 x immunology outpatient appointment, 1x genetic test (Primary immune deficiency syndromes 206 exome panel). Utility decrement associated with a false positive applied as a minimal proxy for parental anxiety arising from uncertainty.
Inconclusive – Died	**Disbenefit / No / Neutral benefit**	Disbenefit / No / Neutral benefit	Y	N	No	No	Assume if a patient dies then they would have had additional testing in the absence of screening. DRG discussion suggested, in some cases there may be parental benefit where testing has led to a cause of death (see category below) in others there may be a disbenefit where the cause of the positive TREC result is unknown.

		Parental benefit	Y	N	No	Possible benefit not included in model	
Died	**Non SCID & inconclusive deaths**	Non SCID & inconclusive deaths	Y	N	No	No	

Appendix 4.1: Immunology costs outpatient



Appendix 4.2: Immunology costs inpatient